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DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, EDUCATION, AND RELATED AGENCIES APPROPRIATIONS FOR 1991

HEARINGS

BEFORE A

SUBCOMMITTEE OF THE

COMMITTEE ON APPROPRIATIONS
HOUSE OF REPRESENTATIVES

ONE HUNDRED FIRST CONGRESS

SECOND SESSION

SUBCOMMITTEE ON THE DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, EDUCATION, AND RELATED AGENCIES

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PART 4B

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DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, AND EDUCATION, AND RELATED AGENCIES APPROPRIATIONS FOR 1991

THURSDAY, MARCH 15, 1990.

NATIONAL EYE INSTITUTE

WITNESSES

DR. CARL KUPFER, DIRECTOR
DR. WILLIAM F. RAUB, ACTING DIRECTOR, NIH
EDWARD McMANUS, DEPUTY DIRECTOR, NEI
DR. JOHN A. McLAUGHLIN, ASSOCIATE DIRECTOR FOR EXTRAMURAL AND COLLABORATIVE PROGRAMS, NEI
KENNETH O. COOKE, EXECUTIVE OFFICER, NEI
FREDETTE WEST, BUDGET OFFICER, NEI
DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DHHS
DHHS

Mr. NATCHER. At this time we take up the budget request for the fiscal year 1991 for the National Eye Institute. We have before the committee, Dr. Carl Kupfer, the director. Doctor, it is a pleasure to have you back before the committee again. Before you give your statement, tell us who you have with you there at the table.

Dr. KUPFER. Yes, sir, it would be my pleasure. To my far left is Kenneth O. Cooke, the Executive Officer. Next to him is Fredette West, our Budget Officer, and to her right is Mr. Edward McManus, Deputy Director of the Institute. To my right is Dr. John McLaughlin, Associate Director for Extramural and Collaborative Programs.

OPENING REMARKS

Mr. NATCHER. Thank you very much. We will be pleased to hear from you.

Dr. KUPFER. If I may, I will submit my written statement for the record and spend a few minutes making some opening comments.

Mr. NATCHER. You may insert it in its entirety.

Dr. KUPFER. Thank you. Vision research continues to provide new information that increases knowledge in such broad fields as the cause of cancer, regeneration in the central nervous system—which is particularly of importance since we are embarking on the Decade of the Brain—and prevention of the complications of diabetes.

RETINOBLASTOMA GENE

There have been impressive gains in retinoblastoma, (RB) a cancer of the eye that can be fatal. Last year, I mentioned the finding by NEI grantees that the cancer retinoblastoma is caused by the absence of a gene rather than the presence of an oncogene which is the usual cause of an inherited cancer. This RB gene, being absent, does not apparently produce a substance which inhibits tumor growth.

Further research has shown that if one puts the RB gene back into cancer cells that are growing in tissue culture, one can convert those cancer cells into normal cells with normal growth characteristics. The RB gene also has been shown to play a role in other cancers, including cancer of the breast, lung, and bone. Just in the last two weeks, there was a very interesting article appearing in the scientific literature, describing how one of the National Eye Institute's grantees has been able to place the RB gene into prostate tumor cells in tissue culture and convert the cancer cell into a normal cell. The implications of this finding to the whole field of cancer biology is just beginning to become known.

CENTRAL NERVOUS SYSTEM REGENERATION

A second area of great interest has been the question of regeneration in the central nervous system. The eye, in particular the retina, is part of the central nervous system. I mentioned last year that one of our research grantees wanted to do some regeneration experiments in the spinal cord.

He was able to show conclusively that after a crush of the spinal cord of laboratory animals it was possible to induce new fibers to bridge the crushed area. These new fibers were then able to set up connections that enabled the previously paralyzed high limbs of animals to regain movement.

Applying the results of these experiments to the eye, other researchers have been able to show that one can transplant portions of the retina, specifically the tissue called the retinal pigment epithelium which underlies the retina, and then the photo-receptors, the cells that convert light into electric impulses. These cells can be transplanted and they survive. This now offers the very exciting possibility that certain retinal degenerations, as well as degenerations further up in the central nervous system, may be reversible.

DIABETIC RETINOPATHY

The third area I would like to highlight is the recent conclusion of a clinical trial, the Early Treatment Diabetic Retinopathy Study. This trial had three purposes. One was to determine whether a form of decreased vision occurring in diabetics when fluid gets in the macula—the area of the retina associated with sharp, central vision—could be prevented by the use of laser treatment. The study showed that we can reduce this decrease in vision by some 50 percent with the use of the laser.

A second concern was whether early laser treatment could improve our ability to prevent blindness from diabetic retinopathy. This is important because obviously if it were advantageous to

treat early, we would be offering treatment to every diabetic patient who developed the earliest signs of retinopathy. This would not only require many patients to make an important treatment decision early in the course of their disease but from an economic standpoint would have a major impact indeed.

The result of the study has shown that it is perfectly appropriate to wait until the disease is much more advanced. The results are just as good with later treatment as compared to early treatment. We now know that we can follow these patients very closely and wait until what we call high-risk characteristics develop in the eye before treating without losing any chance of preventing severe visual loss.

The third aspect of the trial was to determine whether aspirin would have any beneficial effect on slowing the development of diabetic retinopathy. The trial showed that aspirin did not have a beneficial effect, but what was even more important was that it showed that diabetics can take aspirin without running an increased risk of having bleeding into their eye. This is important because we know that diabetics are at twice the risk for cardiovascular disease than non-diabetics, and we also know that aspirin is of some value in reducing this risk from cardiovascular disease.

We can now say to diabetics it is safe to take aspirin, there will be no danger of increased hemorrhage in the back of your eyes. These are some of the research highlights of the past year.

The fiscal year 1991 request is $247,392,000. I would be pleased to answer questions.

Mr. NATCHER. Thank you, Dr. Kupfer.

[The information follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Eye Institute

Mr. Chairman and Members of the Committee, it is always gratifying for me to be able to tell you about progress in vision research supported by the National Eye Institute (NEI). Over the years this progress has been significant even though confirmation of new research findings is sometimes a long and arduous task. This year, however, I am especially happy to tell you about several research findings that either strengthen or confirm earlier scientific hypotheses reported in this same forum in the past two or three years.

Three years ago, I told you about NEI-funded researchers who identified, cloned, and characterized the defective or missing gene that leads to retinoblastoma (RB). RB is a cancer of the eye that occurs in children who often later develop other cancers. RB can mean loss of the eye or even death. This was the first time that the cause of a cancer was found to be a partial or complete loss of a gene that normally produces a protein to suppress tumor growth. Using this finding, the researchers then developed a blood test that can be used to determine whether a child in a family with a history of RB has inherited the RB gene from a parent.

More recently, other NEI-funded scientists inserted clones of a healthy RB gene into RB tumors grown in laboratory cultures. The tumors stopped growing and the cells began to differentiate into normal tissue. This work confirms the suppressor gene hypothesis and suggests that gene therapy for RB may be possible.

Although this molecular genetics research has pinpointed the cause of the cancer, a major obstacle in RB research has been the lack of an animal model to study the dynamics of how benign cells in the eye become malignant. Now, however, NEI grantees have developed a line of mice with inherited eye cancers that are the same as human RB in cell type, structure, biochemistry, and in the way the malignancy develops. With the mouse model, we can study the process of malignant transformation from inception through proliferation and metastases. The model should also be valuable for developing and testing drugs to counteract the lack of the control protein.

In another area of basic research, scientists are making rapid progress in replacing deteriorated cells of the retina with healthy cells. Last year I reported that researchers had taken strips of pigment epithelial (PE) cells from newborn rats and transplanted them into damaged retinas of adult rats with a genetic mutation that progressively destroys the light-sensitive photoreceptors. PE cells ensure the proper functioning of photoreceptor cells by supplying nutrients and removing waste products from them. The transplanted PE cells stopped the degeneration and rescued populations of nerve cells that otherwise would have died from the inherited disease. Other NEI-funded researchers have now transplanted the photoreceptor cells

themselves, which survive transplantation and appear to be metabolically active for at least six weeks.

In immune studies that complement this transplantation work, NEI intramural researchers are developing molecular probes to isolate the specific protein on white blood cells that is likely to cause graft rejection. If the protein is identified, the investigators will begin to devise ways to neutralize its immune action. This type of concerted, creative research offers hope that one day we may be able to rescue or replace degenerating retinal cells in diseases such as macular degeneration and retinitis pigmentosa.

Retinitis pigmentosa (RP) is a group of inherited retinal degenerative diseases that affect otherwise healthy teens and young adults. RP types differ in several ways--inheritance pattern, time of onset, severity, and progression--but all have the same end-state of blindness. In addition to the cell transplantation work, vision researchers are making progress on two other fronts--identification of a biochemical error outside of the eye in one type of RP and a specific genetic defect in another type.

National Eye Institute intramural biochemists have been studying a breed of highly inbred poodles that naturally develop a retinal degeneration similar to human RP. This disease is caused by a recessive gene found in the non-sex cells of both parents. The researchers found that, in both healthy and affected dogs, the rod photoreceptors cells produce only very small amounts of DHA, a fatty acid that is needed in high levels to maintain the health of the highly active rods. This suggested that some other organ, probably the liver, produces the required high levels of DHA, which is then delivered to the eye. When the dogs' blood was tested for the presence of DHA, they found that the affected dogs, but not the healthy dogs, had very low levels of circulating DHA. Other researchers had found that blood levels of DHA are also low in RP patients who have the recessive type of RP, thereby supporting the theory of a biochemical error in an organ other than the eye. The next logical step is to determine whether a dietary supplement of DHA can slow or halt disease progression in the dogs.

Molecular genetics research on RP is also making great headway. Within a year after one NEI-supported scientist had mapped the gene for the dominant form of RP to an area of chromosome 3, another group of NEI grantees identified and characterized the specific gene that produces a protein called rhodopsin. Rhodopsin is the protein that enables photoreceptors to respond to light. From earlier NEI-funded research, the scientists already had blood samples from about 1600 RP patients to begin immediate study of genetic patterns in the mapped chromosomal area. In 17 of 148 of their samples from unrelated dominant-type RP patients, they found a transposition of just two DNA elements on the gene that normally produces rhodopsin. Because of this transposition, the scientists believe that the aberrant gene codes for a disfunctional rhodopsin. None of the unaffected controls and only a small subset of the dominant RP patients had this transposition, further showing how varied are the retinal degenerations we cluster under the term RP. I think that these research advances nicely illustrate the importance of interaction

among various scientific disciplines.

During this past year, we have also gotten results from clinical studies of treatments for glaucoma and diabetic retinopathy. The Fluorouracil Filtering Surgery Study is a multicenter, randomized study investigating whether postsurgical injections of the drug 5-fluorouracil, or 5-FU, would increase the success rate of glaucoma filtering surgery. Creation of a surgical drainage channel, or filter, is standard treatment for patients whose elevated intraocular pressure can no longer be controlled with drugs. 5-FU was used in the expectation that it would impede the growth of scar tissue that sometimes blocks the surgically created channel, thereby necessitating another filtering operation that has even less chance of success.

Early study results show that one year after surgery, only 27 percent of the patients who received 5-FU needed reoperation, compared to 50 percent of those who had surgery alone. Moreover, in the surgery alone group, only about one-third could maintain satisfactory intraocular pressure without medications, compared to two-thirds of those receiving 5-FU. Furthermore, of the patients needing medication, those in the 5-FU group needed lower doses and fewer types of medication than did those who had surgery alone. The next steps are to study the long-term safety and efficacy of the drug.

To improve the outcome of treatment for diabetic retinopathy, which treatens the sight of the 11 to 12 million Americans with diabetes, the NEI initiated the Early Treatment Diabetic Retinopathy Study (ETDRS) in 1979. The ETDRS was designed to investigate three questions: Is laser treatment effective for diabetic macular edema, which is a swelling of a part of the retina that provides sharp, straight-ahead vision? When in the course of the disease progress is the best time to begin laser treatment for diabetic retinopathy? Does aspirin treatment alter the progression of diabetic retinopathy? The controlled, multicenter clinical trial, begun in 1979, enrolled 3,711 patients at 22 centers.

Final results support earlier study findings that laser treatment of macular edema reduces by half a patient's risk of visual loss. The study also showed that, if a patient with early diabetic retinopathy is followed regularly, laser treatment may be safely deferred until the disease progresses to a more advanced stage, thereby sparing the patient from the possible siade effects of treatment until sight is threatened. It also showed that although 650 mg of aspirin taken daily did not prevent or slow the progression of retinopathy, neither did it increase the risk of progression. This latter finding may be important to diabetic patients who have twice-the-normal risk for developing cardiovascular disease, which might require daily aspirin therapy.

In closing, I would like to describe work in two areas of research that are important for future vision research. We know that certain eye diseases are related to the aging process, but we lack accurate and current information about the prevalence of blindness and visual impairment among older people. The Baltimore Eye Survey was funded to provide this information by studying a large, multiracial population that could serve as a model for many

urban areas in the United States.

The survey determined the prevalence of blindness and visual impairment among blacks and whites 40 years and older who come from comparable socioeconomic settings. A population-based sample of 5300 blacks and whites received an ophthalmologic screening examination that included detailed visual acuity measurements. From this sample, the researchers estimate that more than 3 million Americans 40 years or older are visually impaired and 890,000 of these are bilaterally blind.

The survey found that prevalence of blindness and visual impairment in blacks was double that of whites. The rates of vision loss for both groups rose dramatically with age, but there was no difference between males and females in the rise. The researchers also found that more than 50 percent of the subjects had improved vision after refractive correction, some improving by three or more lines on the eye chart.

In the older segment of the population, the need for cataract surgery will constantly expand as more and more people enter their 70s and 80s. Currently, cataracts cause visual disability for about 20 percent of Americans in their 70s and for about 50 percent for those in their 80s. Americans annually spend about $3.5 billion to have cataracts removed. We calculate that if some way could be found to delay the need for surgery by just 10 years, the annual number of cataract operations could be cut in half at a significant annual savings to the Nation. Cataract prevention, therefore, is an important NEI research goal.

Currently, several drugs are showing promise for slowing or halting the development of cataract, but, until recently, we have lacked a reliable method for classifying subtle differences in lens opacities. Such a method would be essential for monitoring the effectiveness of a candidate drug. Now NEI scientists have developed a Lens Opacities Classification System that makes it possible to grade/classify cataracts accurately and pinpoint fairly subtle lens changes.

Because the new system is easy to use and users reach almost perfect agreement on cataract classification, it should also be valuable for field studies of cataracts in various parts of the world. Investigation of questions about whether altitude or sunlight affect cataract development may provide important clues about mechanisms involved in cataract development and may lead to methods of prevention. These are but a few examples of how our investment in vision research is producing significant returns in clarifying the underlying process of several blinding eye disease and in advancing our ability to prevent blindness.

Mr. Chairman, the FY 1991 budget request for the National Eye Institute is $247,392,000. I will be happy to answer any questions.

KUPFER, DR. CARL
Director, National Eye Institute
February 9, 1928. New York, New York.

Education: A.B., Yale Univ., 1945-48. M.D., The Johns Hopkins Medical School, 1952 Certified. Amer. Bd. of Ophthalmology, 1958.

Professional History: Internship and Assistant Residency, Wilmer Eye Inst., Johns Hopkins Hospital, 1952-54. Lab. Assistant, Biostatistics, Johns Hopkins School of Medicine, 1953-58. Research Fellow in Ophthalmology, Harvard Medical School, 1958-60. Instructor in Ophthalmology, Harvard Medical School, 1960-62. Asst. Prof. of Ophthalmology, Harvard Medical School, 1962-66. Prof. and Chairman in Ophthalmology, Univ. of Wash. School of Medicine; Research Affiliate, Univ. of Wash. Primate Ctr., 1966-70.

Professional Organizations: Amer. Physiological Society; Assoc. for Research in Vision and Ophthalmology; American Academy of Ophthalmology; American Ophthalmological Society; Pan American Ophthalmological Society; Johns Hopkins Univ. Soc. of Scholars; Member, Inst. of Medicine, National Academy of Sciences.

Honors and Awards: The Secretary's Special Citation, Dept. of Health, Education and Welfare (DHEW), 1972; The Superior Service Award, DHEW, 1974; Presidential Rank Award of Meritorious Exec., 1983; Migel Medal, Amer. Foundation for the Blind, 1976; Public Service Award in Ophthalmology, Amer. Acad. of Ophthalmology and Otolaryngology, 1977; Special Award of Honor, The Assoc. for Research in Vision and Ophthalmology, 1983; David Rumbough Memorial Scientific Award, The Juvenile Diabetes Found., 1983; The Lighthouse Pisart Vision Award, 1984; Cavera Medal of Univ. of Rome, 1985; The Mildred Weisenfeld Award for Excellence in Ophthalmology, 1987. Dunphy Lecture, 1977; Lorand V. Johnson Lecture, 1980; C. Dwight Townes Memorial Lecture, 1981; Glenn A. Fry Award Lecture, Amer. Acad. of Optometry, 1981; Richard Stein Lecture, Maurice and Gabriella Goldschleger Eye Inst., Tel-Aviv Univ., Sackler School of Med., Israel, 1982; Jules Stein Lecture, L. A., Calif., 1983; Bowman Lecture, The Ophthalmological Soc. of the U. K., London, England, 1984; Seymour Roberts Memorial Lecture, Stanford Univ. Med. Ctr., Stanford, Calif., 1984; Doheny Lecturer, Univ. of So. Calif., 1984; Everett Kinsey Lecturer, Contact Lens Assoc. of Ophthalmologists and Internat'l Soc. for Refractive Keratoplasty, Las Vegas, Nevada, 1987. Editorial Bd, Investigative Ophthalmology, 1969-77; Editorial Bd, American Journal of Ophthalmology, 1971-83; Mbr, Scientific Advisory Committee, Fight for Sight, 1971-present; Mbr, Nat'l Diabetes Advisory Board, 1976-present. Mbr, Board of Trustees, Helen Keller Internat'l Inc., 1975-pres't; Coord. U.S.-Japan Collaborative Agreement in Vision Research, 1976-present; Mbr, Internat'l Vitamin A Consultative Group, WHO, 1973-pres't; Mbr of U.S. Delegation to World Health Assembly, 1978; Mbr, WHO Advisory Group for Prevention of Blindness Prog., 1978-84; Consultant, Pan American Hlth Org., 1978-pres't; Coord. for USA, Priority Area "Eye Diseases," U.S.-U.S.S.R. Prog. for Health Cooperation, 1978-pres't; Mbr, WHO Expert Advisory Panel on Trachoma and Prevention of Blindness, 1979-pres't; Dir., WHO Collaborating Ctr. for the Prevention of Blindness, Nat'l Eye Inst., Bethesda, MD, 1979-pres't; Pres., Internat'l Agency for the Prevent. of Blindness, Oct. 1982-present.

DISTRIBUTION OF RESOURCES

Mr. NATCHER. Now, as Dr. Raub knows full well, each of the institutes approaches its assignment somewhat differently. The Eye Institute has the reputation of one of the best managed in the National Institutes of Health.

Tell us, Doctor, how your institute is different in terms of its use of grants, centers and contracts. How do you differ?

Dr. KUPFER. Mr. Chairman, many years ago in conjunction with our National Advisory Eye Council we embarked on a very intensive program planning process. In the course of this process, we developed certain philosophic principles as to how the National Eye Institute should function. These principles have really been the keystone of our program since the early 1970's.

The first decision made was that we would put most of our resources into the investigator-initiated research project grants. Therefore, almost all our extramural research grant dollars, about 90 percent, are designated for individual investigator initiated research project grants. Of course these researchers compete nationally and must recompete every three or five years.

We are certain the quality of this research is as high as it can possibly be. Once having made the decision to emphasize research project grants other things followed. We knew we would not have any program project grants, which are large umbrella grants that bring in a large number of investigators. For the vision research community this has worked very effectively. In addition, we decided that we would not fund large multi-dimensional center grants. In a sense, we have replaced those with small core grants which enhance the research capability of at lease five or six individual researchers in an institution.

Now, if we have perhaps 10, 15 or 20 investigators, all with their own research grant in a university setting, this to a certain extent represents a center of excellence. We don't support them with a center grant; however, since they do have their own individual research grants, we can very often provide them with a small core grant that provides central resources which they can all share.

Finally, we have restricted our contract program to selectively support specific clinical trials in which the institute itself, through its Biometry and Epidemiology Program has a very major role in the development of the protocol and seeing it through.

In summary, almost all of our extramural dollars are in investigator-initiated research project grants. Our contract program is very small and targeted to the support of clinical trials.

AWARD RATES

Mr. NATCHER. Your practice, Doctor, of putting a larger portion of your budget into project grants has allowed you to fund more of your approved applications. What can you tell us about your approval rates and what this means in terms of the relative quality of your grants?

Dr. KUPFER. Sir, last fiscal year, we awarded 47 percent of the approved grant applications. In 1990, the award rate is estimated to be about 42 percent and the 1991 estimate is about 38 percent. These figures must be analyzed in a variety of ways. As the

number of approved grants increases, then the percentage of funded grants may decrease. Therefore, we are very much involved in looking at the cost elements of grants to determine how we can most efficiently utilize the funds in a particular grant to produce the maximum amount of research results. That is a much more useful way of assessing how well we are using our resources rather than only looking at the funding rate.

GRANT COST STUDY

Mr. NATCHER. All the institutes have problems, as you know, with the increasing size of grants. I understand you have begun a review of the reasons for this so that these costs can be kept under better control. Do you have any preliminary results from this study?

Dr. KUPFER. The study is on-going. We will probably be in a very good position, sir, at the hearings next year to give you results. However, I can say that at the present time, the average cost of a research grant in the National Eye Institute is the lowest at NIH.

Mr. NATCHER. Dr. Raub, we have been talking a lot as you know about levels of downward negotiations which I think everybody in this room finds objectionable. Part of the problem is the size of the average increase being requested by the researchers themselves. We have figures of 25 to 50 percent increases. What can you tell us about this problem, Dr. Raub?

Dr. RAUB. Mr. Natcher, those increases occur typically at the time of either the first presentation of the grant application or in the so-called competing renewal request where the scientist has every incentive to put forward the set of cost estimates that he or she thinks best serves that problem. As the project goes on, there has been a decline in the relative availability of funds from other sources such as foundations.

There have been increases in the costs of salaries in the academic community especially as well as increasing costs for equipment and space. We tend to see the concentration of those costs occur when the competing renewal applications come in.

Mr. NATCHER. Thank you, Dr. Raub.

Mr. Stokes, I yield to you.

GLAUCOMA—BALTIMORE STUDY

Mr. STOKES. Thank you, Mr. Chairman.

Dr. Kupfer, in your written remarks to this committee you state that the Baltimore eye survey found the prevalence of blindness and vision impairment in black Americans was double that of whites. How do you explain this?

Dr. KUPFER. Mr. Stokes, we have been very much interested in glaucoma among blacks. We have always had the feeling that it was much more prevalent and now we are really obtaining the data that proves that point, not only in the Baltimore eye study but in a study we are conducting in Barbados as well.

There are two possibilities for this increased prevalence. One is that we are dealing with the same sort of glaucoma that appears in whites, but, it is more virulent, that is it begins at an earlier age and progresses more rapidly. The other possibility is that it is a dif-

ferent form of the disease. We are trying to separate those two concepts by looking at what the risk factors are for glaucoma in blacks as compared to those in whites. If they are the same, then we are dealing with the same disease but for various reasons it appears to be more virulent. If the risk factors are different, then perhaps we are dealing with a different disease and must use different approaches.

GLAUCOMA—ACCESS TO CARE

Mr. STOKES. You have also stated that more than 50 percent of the subjects had improved vision after refractive correction. This would seem to indicate that there is some relationship between good vision and having access to care, would it not?

Dr. KUPFER. Yes, sir, you are absolutely right. This is a very important finding because if we can improve vision in 50 percent of these individuals just by fitting them with glasses, it is very clear that we must improve our availability of health care in this respect.

Mr. STOKES. Is there any manner in which the Eye Institute can address this particular disparity?

Dr. KUPFER. One possibility would be to employ educational approaches to make people more aware of what is available. We must keep in mind that this study was done not very far away from some of our leading hospitals in Baltimore. There must be increased awareness upon the part of the public. Of course, the National Eye Health Education Program has as one of its major goals the increased awareness upon the part of Americans as to the eye care facilities that are available.

PREVALENCE OF EYE DISEASES/DISORDERS

Mr. STOKES. The Baltimore eye survey was a good step in determining the prevalence of eye conditions in older people. What is NEI doing to gather data on prevalence of visual impairment in the general population?

Dr. KUPFER. We are pursuing a study in Framingham, Massachusetts. We did an initial eye study in Framingham a few years ago, which was based on the excellent program done there by the National Heart, Lung, and Blood Institute. The first study of prevalence in the general public was done in 1973. We are now repeating that study to see not only what has happened to prevalence since that time but even more important, look at incidence, that is the number of new cases occurring. We are also going to be looking at the offspring of those in the Framingham study to determine the prevalence of eye disease in the next generation.

There are other sources of information, including the National Health and Nutrition study conducted by the National Center for Health Statistics every five years. We are able to bring into that study questions about eye health and disease and also conduct an examination of the eye so that we have some other source of looking at the American population across the board. Finally, we are also trying to determine through the National Eye Health Education Program what are the attitudes of individuals toward eye health, what is the knowledge in the community and how we can

best influence that by trying to educate the American public about what they can do to keep their eyes healthy.

LOW VISION

Mr. STOKES. Dr. Kupfer, what exactly is low vision?

Dr. KUPFER. That is an excellent question. Let me say that normal vision is 20/20 and what that means is that there is a line of letters on the eye examination chart which if it can be read at 20 feet, the usual distance in an eye chart examination, then vision is considered normal.

The top letter on the chart can be read by someone with normal vision at 200 feet, however an individual who is visually impaired may need to be as close as 20 feet away to read it. That is called 20/200 vision. The legal definition of blindness is a visual acuity of 20/200 or less. The individual can just read the top letter on the eye chart or can not read it at all at 20 feet. Driving an automobile, being able to read a newspaper comfortably, and many other activities that occur in our industrial society requires a vision of at least 20/40 which is two lines above the 20/20 line on the chart.

Low vision is thus defined as vision that is less than 20/40 but better than 20/200. It is not as bad as legal blindness and it is not as good as 20/20. That is the range where many Americans have problems because less than 20/40 means they cannot receive a driver's license. They may not be able to hold down a job; yet they are usually able to move about for a variety of daily activities.

Mr. STOKES. Are we doing any type of research in that area?

Dr. KUPFER. Yes, sir. This is a very high priority area for us. We are supporting a number of grants to try to find the best ways to determine how these individuals can maximize their residual vision. This is done through telescopic lenses and through various kinds of reading machines. Through color-coding of objects the need to resolve very small detail can be avoided in certain cases. In our present program planning activities we are placing major emphasis on low vision research. As a matter of fact, a meeting of our Low Vision and Rehabilitation program planning panel is being conducted today in Minneapolis.

I mentioned last year that the Wilmer Eye Institute of Johns Hopkins University is collaborating with NASA to develop high technology instrumentation to allow individuals with low vision to be able to get about in a much more effective way. The development of reading machines that not only magnify print but convert it into the spoken word has moved forward very, very rapidly.

TECHNOLOGY TRANSFER

Mr. STOKES. Doctor, in the area of diabetic eye research, what are you doing to be able to get information to ophthalmologists and optometrists out in the field?

Dr. KUPFER. We have just concluded the results of a 10-year study on the early treatment of diabetic retinopathy where we conclusively show that one form of decreased vision, that resulting from the collection of fluid in the macula which is the area of the retina that produces sharp central vision, can be prevented in 50 percent of cases by the use of laser.

We now know that we can follow diabetics until they develop certain high-risk characteristics before treatment is indicated. This information has been disseminated widely to ophthalmologists and optometrists by direct mailings, by presentations at professional meetings, and by presentations to the press at press conferences throughout the country. Because it is not only important to have the message conveyed to the practitioner but also to the public, we are also making this a very important component of the National Eye Health Education Program. If the public is well informed, people will be in a better position not only to receive this information from their physicians but to act upon it. Compliance is a very major problem in having patients take advantage of whatever therapeutic modalities are available.

TRAINING

Mr. STOKES. Doctor, do you think we are training an adequate number of ophthalmologists and optometrists as clinical researchers?

Dr. KUPFER. We continue to be heartened by the fact that there is a small but steady stream of research ophthalmologists and optometrists coming into the field. We are using a variety of mechanisms to attract even more. I am at the moment satisfied with the rate of their coming into the field. However there is a second aspect, and that is once they come into the field, to be able to keep them in research. There are a number of considerations that come to mind with regard to that aspect of the problem.

Mr. STOKES. Thank you, Doctor.

Thank you, Mr. Chairman.

Mr. NATCHER. Mr. Early.

ADVANCES IN EYE RESEARCH

Mr. EARLY. I don't know of any health problem I am more fearful of than loss of eyesight. The National Eye Institute has probably contributed more to improving eye health than any other entity. I know people who have glaucoma who have told me of conditions that were not treatable 10 years ago but are treatable today.

You mentioned retinoblastoma. It is so exciting that something can be done if a youngster has that disorder. What would you say is the greatest advance in eye research over the last 20 years?

Dr. KUPFER. I will focus on the greatest advance in terms of laboratory research and the greatest advance in terms of clinical research. From lab research, it is the retinoblastoma story, not only because it relates to a devastating and often fatal eye tumor but because the ramifications of this research extend into the entire field of cancer biology. I commented earlier that a clinician supported on one of our Physician Scientist awards has demonstrated that the retinoblastoma gene also appears to be missing in cancer of the prostate. If one takes this prostate tumor cell and inserts the retinoblastoma gene, one can convert this cancerous cell into a normal prostate cell.

Mr. EARLY. How is that different from what we talk about with CF? Isn't that just telling people you identified the gene? You are

telling people what you are doing with it. People don't care about identifying the gene. People care about getting the problem corrected. I think that is a nice story.

Dr. KUPFER. The next part then is to demonstrate how one can convert this laboratory knowledge into a clinical intervention.

Mr. EARLY. I think that is the most important thing.

Dr. KUPFER. From a clinical standpoint the greatest and most exciting advance in my opinion has been the result of our Diabetic Retinopathy Study in which we showed that laser treatment could reduce by 60 percent the rate at which diabetics become blind from this eye complication.

ECONOMIC SAVINGS

Mr. EARLY. Can you give us an idea of some of the cost savings that have been the result of the work supplied by your institute?

Dr. KUPFER. The diabetic retinopathy study had been the one most examined from this point of view. We had a health economist come and examine the data. You will recall the study cost about $11,000,000. That of course goes back to 1976. A conservative estimate excluding the cost of lost production, is that nearly $270,000,000 will have been saved between 1976 and 1996. This span of time is the period for which we expect this therapy to be the major way of reducing blindness from diabetic retinopathy.

Mr. EARLY. Would you provide for the record, the cost savings for glaucoma and some of the other eye disorders.

Dr. KUPFER. I will be pleased to.

[The information follows:]

ECONOMIC COST SAVINGS

At this point in time, we have not done as detailed a cost/benefit analyses for glaucoma and other eye diseases as we have done for diabetic retinopathy. However, in the proposed Quality of Life in Glaucoma Management clinical trial, functional status and life satisfaction would be measured and compared in two groups of patients with newly-diagnosed open angle glaucoma. This cost-effectiveness analysis will include a focus on the costs of; various treatments; physician visits and hospitalizations; morbidity; time lost from economic or other activities; and mortality pattern of the medical versus surgical group.

With regard to vision research in general, we have prepared some estimates to give us an idea of the economic return on the investment. One of these analyses showed that the use of laser treatment in place of conventional surgery for angle-closure glaucoma would save approximately $66 million per year. The savings resulting from the use of laser therapy for the "wet" or neovascular form of aging-related macular degeneration has been estimated to be nearly $57.5 million per year. A preliminary analysis of the savings from the Cryotherapy for Retinopathy of Prematurity (ROP) Study has shown that the net present value cumulative savings from this treatment may be approximately $920.8 million over the next 65 years, for children affected with ROP, or nearly $14.2 million per year. It should be remembered, however, these cost analyses do not take into account the years of vision gained or improvement in the quality of life that may be the most important benefits offered by these treatments.

GREATEST NEED IN EYE RESEARCH

Mr. EARLY. What is the greatest need in eye research in the future?

Dr. KUPFER. The greatest need is to capitalize on the very rapid development of molecular biology as it applies to the central nervous system. As we embark on the Decade of the Brain. There are

many opportunities to learn more about how the brain functions by examining the visual system which is in a sense the easiest sensory system to examine. If we understand how the visual system works, we would understand how all the other aspects of the brain operate. The major challenge at the present time is to take advantage of those opportunities.

DECADE OF THE BRAIN

Mr. EARLY. We are doing it rhetorically. I am not sure we are doing it with our pocketbooks, Doctor. So eye research is involved in the Decade of the Brain. Are vision researchers a significant component of the neuroscience researchers?

Dr. KUPFER. Yes, sir. Thirty-eight percent of the nerves that go into the brain come from the eyes. If we stop to think about how much we depend on vision, it is even more evident. When we hear something, we turn to look where the sound is coming from. If somebody touches us, we turn to see what is happening, even if we smell a fragrance in the air, we turn to look. We depend very heavily on the visual system. By studying the visual system, we can easily measure both the stimulus and the response. Light is going in and eye movement is coming out. We can measure that very precisely.

LASER TREATMENT

Mr. EARLY. Are you doing enough with lasers?

Dr. KUPFER. There is no doubt that lasers have moved very rapidly into the treatment of many eye diseases. The future of lasers will be not only in treatment but in diagnosis. There is a group of lasers called excimer lasers that do not destroy tissue by heating or by shock, which is the usual way lasers destroy tissue, but by destroying one cell at a time. One can do very fine surgery on tissue using excimer lasers.

Mr. EARLY. Will you provide some additional information for the record on that?

Dr. KUPFER. Yes.

[The information follows:]

EXCIMER LASER

The excimer laser has emerged as the latest development in the application of laser technology to ophthalmology. The word "excimer" is derived from "excited dimer", which describes the fact that the energy of this laser results from the combination of an inert gas with a halogen compound. A strong electric current is used to drive the reaction of these substances to form a short-lived, unstable molecule that emits very energetic radiation as it returns to the ground state. This energy can be effectively controlled and focused to destroy small areas of tissue. The excimer is referred to as a "cool laser" because it destroys the chemical structure of biological tissue, rather than burning the tissue as other lasers do. The advantage of this procedure is that it can be controlled to carve away layers of cells. Widespread application of the excimer laser will require first additional research on its short- and long-term effects. Investigators have found, for example, that they are limited by major gaps in the understanding of some of the fundamental biologic processes that control the shape of the cornea and the response of this tissue to laser surgery.

STRATEGIC DEFENSE INITIATIVE

Mr. EARLY. Hasn't a lot of money come out of SDI moneys?

Dr. KUPFER. That very well may be. I will have to provide that for the record.

[The information follows:]

STRATEGIC DEFENSE INITIATIVE SPINOFFS

Certainly, laser technology received a boost from the defense associated research. There probably have been some technological "spinoffs" which have contributed to the development of laser instruments that are beginning to be used in the diagnosis and treatment of eye conditions. For example, a number of these devices, particularly the scanning lasers intended for diagnostic purposes, make use of computer-controlled "active" mirrors to generate images and computer-assisted enhancement of the images produced.

CLINICAL TRIAL PRIORITY

Mr. EARLY. What is the single most important clinical trial you believe should be supported in 1991, in your professional judgment?

Dr. KUPFER. There is a glaucoma clinical trial that is in the planning state which we very much would like to initiate in 1991. The purpose of that trial is to determine whether medical therapy or surgical therapy would have a better outcome not only in preserving vision but also in terms of improved quality of life. Quality of life considerations are beginning to play more and more of a role in what we should be doing for our patients.

Mr. EARLY. They should, shouldn't they?

Dr. KUPFER. Yes, sir.

Mr. EARLY. Doctor, would there be a cost effective analysis as part of that study? Have you done any analysis?

Dr. KUPFER. We are now building into all our clinical trials both an economic cost effective analysis as well as a quality of life analysis.

Mr. EARLY. Evidently we are not getting the funds unless we make that type of argument. Would you expand on the cost savings analysis for the record.

Dr. KUPFER. Yes, sir.

[The information follows:]

COST BENEFIT ANALYSIS

The primary goal in treating patients with glaucoma has been to prevent or minimize the loss of visual function. The standard approach to treatment in the United States has been to prescribe medications that reduce the intraocular pressure. When medical management fails, attempts are made to reduce the intraocular pressure using argon laser trabeculoplasty followed, if necessary, by filtration surgery.

Glaucoma patients managed by medical therapy often report serious, disturbing side effects. These include brow ache, ocular irritation, unslightly red eyes, palpitations, fatigue, confusion, loss of appetite, weight loss, poor vision in dim light, and others. In addition, risks of certain medical therapies for glaucoma also include cardiac arrhythmia and blood disorders. Thus, treatments that may be beneficial in terms of reducing intraocular pressure may also have side effects that affect the quality of the patient's everyday life—the patient's ability to perform common tasks and the patient's life satisfaction. Therefore, in treating glaucoma, the ophthalmologist strives to maintain the quality of an individual patient's visual function without causing untoward effects that might offset the benefits of the treatment. Unfortunately, the frequency of patient complaints about side effects, along the well-known problems of patient compliance with glaucoma medications, would appear to suggest that this treatment goal may not always be achieved. In fact, some clinical investigators have reported pilot studies in which new glaucoma patients have been treated immediately with filtration surgery.

In the proposed Quality of Life in Glaucoma Management clinical trial, functional status and life satisfaction will be measured and compared in two groups of patients

with newly-diagnosed open angle glaucoma. Patients in Group I will receive a standard sequence of medications, followed if necessary by laser trabeculoplasty, to control their intraocular pressure; patients randomized to Group II will receive immediate filtration surgery to reduce their intraocular pressure.

This cost-effectiveness analysis will be done using the following data: costs of various treatments; costs of physician visits and hospitalization; costs of morbidity; costs of time lost from economic or other activities; and the mortality pattern of the medical versus surgical group.

DOWNWARD NEGOTIATIONS

Mr. EARLY. What is the downward negotiation for NEI grants?

Dr. KUPFER. In 1990, the downward negotiation is approximately 11 percent.

Mr. EARLY. I asked the other directors about this—that 10 percent was the critical point. That has been the downward negotiation for the last two years for the competing grants, hasn't it?

Dr. KUPFER. We have had many discussions about this with the National Eye Advisory Council. The trade off is to fund enough grants to keep research activities moving. To do that, one has to negotiate downward to free up resources. This is a very difficult balance to strike.

REDUCED NUMBER OF GRANTS

Mr. EARLY. Doctor, this is just my own opinion. I am not a professional but, from listening to the other directors, I would prefer to reduce the number of grants and not have any downward negotiation. What is your assessment?

Dr. KUPFER. Last August, we called together representatives of a number of different organizations involved in vision research. We asked these individuals that very question because we really wanted to have the advice of our community on this difficult topic. There was a concensus that the action taken by the National Advisory Eye Council to negotiate down but maintain an award rate close to 40 percent was the way to go at that time.

Mr. EARLY. Maybe it is for some institutes and maybe it is not for others. What is your basic average grant size?

Dr. KUPFER. It is approximately $155,000. It is the lowest of all the institutes at NIH.

Mr. EARLY. So, a 10 percent downward negotiation is about $15,000 or $16,000. Historically what has been cut out?

Dr. KUPFER. First we look carefully at each grant before we negotiate downward. Some grants can handle such a decrease better than others but on the average it is about 11 percent downward negotiation.

Mr. EARLY. It is not each and every grant?

Dr. KUPFER. No, it is not done across the board. It has to be grant by grant. Some grants just don't have any funds that can be cut to any extent. In other grants the cuts are absorbed however, the rate at which the research is done is reduced. There is no doubt that cutting any grant will impair the rate at which the research can be done.

Mr. EARLY. With a $150,000 grant, if you cut $15,000, you have to be knocking out a major component. How much of that is for salaries?

Dr. KUPFER. Approximately 70 percent is consumed by personnel expenses.

Mr. EARLY. You don't suggest reducing that?

Dr. KUPFER. We try not to.

Mr. EARLY. How can you?

Dr. KUPFER. We try to give consideration to the impact of such cuts on the research being conducted.

Mr. EARLY. 70 percent of the $155,000 amounts to $108,000. That leaves $47,000 for everything else. If you reduce it by $15,000, you are really taking 20 percent of everything except the salaries. I don't know how you do that and still have quality research.

Dr. KUPFER. It is a very difficult decision. That is why we called the grantees themselves in to discuss this. We wanted them to be involved in the decision.

Mr. EARLY. Is there any scientific reason for doing it?

Dr. KUPFER. I don't think this is a scientific question, sir.

Mr. EARLY. Don't give me a scientific answer. Is there any scientific reason for cutting $15,000 of the $47,000 for items other than salary?

Dr. KUPFER. No, sir.

Mr. EARLY. Thank you, Mr. Chairman.

INTRAOCULAR PRESSURE IN GLAUCOMA

Mr. NATCHER. Dr. Kupfer, does everyone have a certain percentage of intraocular pressure as far as the eye is concerned? Is that condition present in all eyes.

Dr. KUPFER. Yes, sir.

Mr. NATCHER. Where are we, Doctor, as far as this pressure and glaucoma is concerned. What is the explanation? Tell me how high as far as intraocular pressure, what would be high?

Dr. KUPFER. Well, if we took 1000 people and measured their pressure we would have a range from say 10 millimeters of mercury to 21 millimeters of mercury. We arbitrarily say that once the pressure is above 22 millimeters of mercury we suspect that this individual may have a problem in the regulation of their intraocular pressure. That is what glaucoma is, a pressure that is too high for the particular eye to withstand. This brings about damage to the optic nerve in the eye.

Mr. NATCHER. Thank you, Doctor.

Mr. Conte, I yield.

GENETIC DEFECTS IN THE BRAIN

Mr. CONTE. Dr. Kupfer, I am glad to see you before our committee this year. Your group has made some fantastic advances in eye research over the years that I have been on the committee. I hope we can continue to maintain the momentum that you started.

As you know, Doctor, 38 percent of the brain's neuronal input comes from the eye—that is why they say: "The eye is the window to the brain." Vision is one of the most precious senses of the body. What are some of the most exciting prospects in visual neuroscience over the next decade, the Decade of the Brain?

Dr. KUPFER. We should begin to take advantage of some of the major advances in molecular biology that can be applied to the cen-

tral nervous system. Recently there has been a new technology developed called the polymerase chain reaction; this will allow a number of research projects to begin. We are also going to be able to develop so-called gene probes that are going to help us understand better how the central nervous system develops.

Obviously, this is going to have an impact on the study of genetic defects in the brain. I might say that 35 percent of all visual disability and blindness is due to genetic defects in the development of the optic nerve and the connections in the brain.

In addition, we will begin to develop what are called transgenic animals to create models of disease in the visual nervous system and the brain. This will give us a powerful way to study diseases that occur in humans and open up the way for development of treatment modalities. We want to extend our early work on regeneration of the optic nerve.

REGENERATION IN THE OPTIC NERVE

We have preliminary evidence that we can bring about regeneration in the retina and in the spinal cord. This was done by vision scientists. Since the spinal cord is very similar to the optic nerve, this research information should be generalizable to the optic nerve. That is a major area of activity.

VISUAL SYSTEM INFORMATION PROCESSING

We are looking at how the brain processes information. We know that there are two channels in the visual system, one that processes information about color and one that processes information about brightness. We want to see how these two interact because if we understand that we would be in a much better position to understand how the brain functions.

ADAPTABILITY OF THE BRAIN

Finally, there is an emerging area of what is called adaptability of the brain. If an adult has a stroke, that person loses quite a bit of function. Whereas, if an infant has damage to the brain, other parts of the brain take over that function. It is very difficult to demonstrate major defects. We want to know why that adaptability is lost in the adult. There is emerging research to show that there are certain transmitters and proteins that are present in the immature brain, if you will, that are lost as the brain matures. Research needs to be done to determine how we can bring those functions back. That is a third area of great excitement.

COLLABORATION WITH NIH INSTITUTES

Mr. CONTE. It is exciting to say the least. How are you going to be involved with your fellow institutes who also share an interest in the Decade of the Brain?

Dr. KUPFER. First of all, we have very close liaison with all the other institutes through an activity called the Inter-institute Genetics Council which occurs on Wednesdays. We usually see patients with genetic diseases. All the other institutes attend. There is enormous collaboration in genetic detection. We are in touch with the Diabetes Institute and their program directors. As a

matter of fact, we are planning to jointly sponsor a meeting in September with the Diabetes Institute on the management of diabetic complications, including diabetic retinopathy.

Finally we will be participating with other institutes in putting together the program of the Decade of the Brain.

USE OF ADDITIONAL FUNDS

Mr. CONTE. I appreciate that. What specific projects that could be initiated in fiscal year 1991 if we had additional funds available.

Dr. KUPFER. Are you referring to the Decade of the Brain type activities?

Mr. CONTE. Yes.

Dr. KUPFER. We would like to follow up as much as possible on the retinoblastoma story. This is one of the most exciting areas that has emerged. It will lead the way into using the techniques developed in molecular genetics into other areas.

One very recent development from the Massachusetts Eye and Ear Infirmary, is the isolation of the defective gene in one form of retinitis pigmentosa. This shows once again how what happens in the lab can be related to a clinical condition.

Lab researchers have long been studying rhodopsin, which is the pigment which captures light in the eyes. We know quite a bit about rhodopsin. Recently its gene was isolated on chromosome 3. And in the last couple of months, one of our grantees found that the gene, a form of retinitis pigmentosa called autosomal dominant also seems to be on chromosome 3.

Two very enterprising researchers at Massachusetts Eye and Ear Infirmary said maybe those two genes are linked. They were able to identify about 150 patients with this autosomal dominant form of retinitis pigmentosa. Tests of these patients' blood samples showed that about 12 percent of these patients had a single amino acid defect in the molecule rhodopsin. This demonstrates the genetic basis for this disease. We know where the defect is. We can now look for other defects in other forms of retinitis pigmentosa patients.

Such studies will open up the entire field of molecular biology of the central nervous system. We want to pursue the development of gene probes for the development of the central nervous system through the polymerase chain reaction methodology. We want to develop the transgenic animals as models for the central nervous system diseases. We want to pursue the regeneration of the optic cell. This is in early development, but, it will have a major impact on restoration of function when function is lost, especially in the adult, and finally to learn about how the brain processes visual information. These are some of the major opportunities that are opening up with the new methods that have been developed. They are all doable.

Mr. CONTE. What you need is additional money?

Dr. KUPFER. To take maximal advantage of all these opportunities, yes.

PROFESSIONAL SALARIES

Mr. CONTE. Salaries for eye doctors are among the highest in medicine. With the increasing pay differential between outside and government salaries, it must be difficult for your institute to recruit and retain top quality senior scientists. Are there any particular areas of eye research which has suffered from this stagnation?

Dr. KUPFER. Wherever there is an opportunity to capitalize on research results obtained in the laboratory by applying them to solving clinical problems we suffer from a lack of critical mass of research ophthalmologists. That is the area where we could do better.

In our own intramural program, we are barely holding our own to take advantage of the research opportunities that are at hand intramurally. We have an active laboratory program. Many results should be applied to the care of our patients. Yet, we are unable to attract the corps necessary to do that. We continue to lose senior personnel. We have not been able to recruit a new senior person for at least 15 years. This is a major concern.

Mr. CONTE. You say you have not been able to recruit a senior person in 15 years. That is really discouraging. Have you had some leave because of salary?

Dr. KUPFER. Yes, we have. We have had several leave because of salary.

RETINOBLASTOMA GENE APPLICATION TO CANCER

Mr. CONTE. Doctor, I hear you made a significant discovery regarding the RB gene in prostate cancer, can you tell us more about it?

Dr. KUPFER. This was reported just a few weeks ago by a young San Diego scientist on a Physician Scientist award from the NEI. He has demonstrated that the same RB gene that is absent in the cancer of the eye, retinoblastoma, is apparently also absent in prostate cancer. If you take that gene and put it into prostate cancer cells in tissue culture, you can convert those cells into normal cells.

The exciting thing about this whole field is that this is the first clear demonstration that it is the absence of a particular gene that allows the cancers to develop rather than the presence of a cancer-promoting gene or oncogene. This has opened up an entirely new area in cancer biology which is being pursued very aggressively. Many researchers are coming to the National Eye Institute wanting to be grantees of the institute because of this very active field.

Mr. CONTE. What would you do, implant those genes into the prostate?

Dr. KUPFER. When normally present, the gene produces a protein. It is that protein that inhibits the development of cancer. We would probably look more toward ultimately identifying the protein and determining how we can turn that protein on in a cancer cell to prevent it from dividing and turn it into a normal cell.

Mr. CONTE. That is fascinating. That is a tremendous breakthrough. Thank you, Mr. Chairman.

COOPERATIVE CLINICAL RESEARCH FUNDING

Mr. NATCHER. Now, Dr. Kupfer, in 1990 you are almost doubling your budget, as you know, for cooperative clinical research, $7,800,000 up to $13,380,000. The original budget request for 1990 made no mention of this. Why have these programs been increased, doctor, what is the reason for it?

Dr. KUPFER. This has to do with the funding, of on-going clinical trials. These clinical trials were originally in the research project grant line and funded as cooperative agreement grants. Then they were moved out of the research project grant line into a separate line as cooperative clinical research. Therefore, a larger figure resulted. figure resulted.

Mr. NATCHER. Doctor, why the increase so much between 1989 and 1990?

Dr. KUPFER. The increase reflects an administrative change within the research grants mechanism. For administrative purposes, we felt that these types of grants had such important public health implications that we moved them out of the research project grant line and into the cooperative clinical grants line. It was just an administrative move. I might add we created a new branch within Dr. McLaughlin's extramural program to manage these types of grants because of the important public health implications that these clinical trials have.

Mr. NATCHER. Doctor, when you get the transcript back, give us a full statement on that.

Dr. KUPFER. Yes, sir.

[The information follows:]

COOPERATIVE CLINICAL TRIALS

One of the major goals of the NEI is to encourage and stimulate high-quality clinical vision research. Particular emphasis is placed on improving the design, implementation, and management of clinical trials. To support the increased demands for management and oversight within this growing program, the NEI established a Collaborative Clinical Research Branch within the Extramural and Collaborative Programs. The new branch has three major functions: to provide overall management for grant, cooperative agreement, and contract-supported clinical and epidemiologic studies; to assist study chairmen and investigators in carrying out review and budgetary functions; and to keep the NEI staff informed of study progress.

The Collaborative Ocular Melanoma Study (COMS) and the Collaborative Corneal Transplantation Study (CCTS) are two large-scale, multicenter, investigator-initiated clinical trials. They were funded originally in FY 1985 for five years using the U01 research project (cooperative agreement) mechanism. However, like most clinical trials in ophthalmology, these studies often require more than five years to complete. The status of the COMS and the CCTS was reviewed at the January 1990 meeting of the National Advisory Eye Council. It was thought that these clinical trials were making good progress toward achieving the original goals. Because the scope, specific aims, and direction of the projects had not changed from what had been originally proposed and approved, the recommendation was that these projects should be extended administratively and with sufficient funds to allow them to proceed as planned. The NEI would now like to provide this funding for the COMS and the CTTS using the U10 Cooperative Clinical Research mechanism (cooperative agreement). This accounts for most of the requested increase in the cooperative clinical research line. As such, there will be no change in the actual research activity that will be supported and no change in the way these projects would be administered by the Institute. It would only entail a change within the designated mechanism of support. It is very unlikely that the NEI will be able to initiate any major new extramural clinical trials in FY 1990.

Clinical trials and other large, fixed-protocol clinical studies have become an increasingly important extramural research activity at the NEI. In FY 1990, we esti-

mate that more than $24 million will be provided for these extramural, investigator-initiated activities. Some of these projects are currently funded using the U01 mechanism and the remainder are funded using the U10 mechanism. We are considering the consolidation of all such funding in the cooperative clinical research line (other research). This should allow for a more coordinated presentation of our extramural activities in this area. This consolidation would facilitate our clinical research planning activities and administrative responsibilities.

CLINICAL TRIALS FUNDING

Mr. NATCHER. The Eye Institute has supported a large clinical trial on diabetes related eye problems for over 10 years. What has been the cost of this study, Doctor?

Dr. KUPFER. It is about $38,000,000.

Mr. NATCHER. How much money is included in your 1991 request for clinical trials? How does this compare for 1989 and 1990?

Dr. KUPFER. For 1991 the budget request includes about $29,000,000 for clinical trials. In fiscal years 1989 and 1990 it was about $29,000,000 also.

LASER THERAPY TO CORRECT REFRACTIVE ERRORS

Mr. NATCHER. We understand your researchers have developed a new laser procedure which may eliminate the need for glasses for a great many people. How safe is this procedure and how soon is it likely to become available to the general public?

Dr. KUPFER. The laser that you are referring to, sir, is called the excimer laser. We have been very interested in this as a way of reshaping the cornea and theoretically doing away with the need for eyeglasses.

However, we are very concerned with how effective this technology will be on reshaping the cornea without causing any complications. Therefore, we have held two workshops to identify the type of basic research we need to do on the cornea to know how it responds to injury, how it heals and what are the factors that would help predict how much of the laser treatment is necessary to correct refractive error. It will be about five years before this treatment would be safe and effective enough to be made available to the general public.

AVOIDANCE OF DUPLICATION OF RESEARCH

Mr. NATCHER. Many of your research proposals have benefits beyond the normal jurisdiction of your own institute. You gave us examples in your statement related to cancer and diabetes. How is this research coordinated in such a way as to avoid duplication?

Dr. KUPFER. In the case of diabetes, we are in close contact with Dr. Gorden and speak to him frequently about our research. Members of our staff serve on the data safety monitoring committee of the Diabetes Institute which is overseeing their clinical trial of tight glucose control versus conventional treatment.We also share information through the National Diabetes Advisory Board and the Diebetes Mellitius Interagency Coordinating Committee. We are involved in setting up a diabetes workshop this September in conjunction with Dr. Gorden and the Juvenile Diabetes Foundation.

In AIDS research we have worked very closely with the National Institute of Allergy and Infectious Diseases. We are embarking on

a large clinical trial on the treatment of the eye complications of AIDS, and the Allergy Institute has been extremely cooperative in gaining the support of their AIDS clinical trial groups and making this trial a high priority for them.

So we feel very confident and feel that there is a tremendous amount of interaction between the Eye Institute and other institutes at NIH.

DEVELOPMENT OF A NEW EYE CHART

Mr. NATCHER. Doctor, I served with a man in the Navy during the war who was totally blind in one eye. In order to receive sea duty assignments he had to pass in both eyes. He memorized the top three lines and had it down to perfection. He always passed. You would eliminate him with the new eye chart which has been developd. He got sea duty assignments. He did not want to sit in New York City.

What can you tell us about their new test?

Dr. KUPFER. The new eye chart we are testing and are very enthusiastic about uses a different principle. The traditional chart has black letters on white background. On that chart the size of the letters becomes smaller and smaller to test how well one can perceive and identify a particular shape. The new eye chart has letters of the same size. However the contrast between the letter and the background becomes less and less. The letters at the top are very black against the white background, but as one moves down, the letters become more and more pale. As such, the difference between the background and letter decreases.

We are now finding that this is a much more sensitive way of assessing visual performance. In addition, I might comment that as a result of our clinical trials, we have developed a new type of eye chart that does use the traditional letters, black letters against white background but has the same number of letters on each line which slowly decrease in size.

Mr. NATCHER. Same letters.

Dr. KUPFER. Yes, but we have two charts: One chart for the right eye and one for the left eye. So your colleague would have been screened out with this particular chart.

Mr. NATCHER. You just eliminated him, Doctor.

Now, doctor, will that chart be patented or copyrighted in a way that will result in substantial profit to whoever developed it? Is this a matter of copyright or patent?

Dr. KUPFER. The chart was developed a few years ago. To the best of my knowledge, it is being commercially produced but is not very expensive. I could provide that information for the record if I may. Thank you.

[The information follows:]

EYE CHART

The high contrast acuity chart was produced by government scientists, as such, it is in the public domain. There can be no copyright for materials developed by the government. It is available through two different sources for $100 or less. The low contrast letter chart is copyrighted and manufactured by a British company. The inventors receive a small royalty for each chart sold. The charts are available for $295 per set from a U.S. distributor. These are clearly not high-profit ventures, but

rather produced in the public interest. Encouraging development of new diagnostic as well as therapeutic devices is an important part of the NEI's mission.

Mr. NATCHER. That is fine.

MACULAR DEGENERATION

Doctor, you testified previously that macular degeneration is a leading cause for blindness in older people. Have you made any progress in the development of more effective treatments for this particular problem?

Dr. KUPFER. There are two types of macular degeneration. The so-called wet type where there are new vessels that grow in the macula and the dry type where the tissues in the macula seem to degenerate. We can treat the wet type very effectively with the laser and reduce by 50 percent the number of people who lose vision. We have not developed an effective treatment for the dry type but we are about to begin a very large clinical trial in which we are looking at the precursors, the risk factors, in the development of macular degeneration.

This study will involve 4000 patients. We are going to be doing a study similar to the Framingham study which determined risk factors in heart disease. We want to study the risk factors in macular degeneration. We will have important findings in a few years on this.

NATIONAL EYE HEALTH EDUCATION PROGRAM

Mr. NATCHER. This committee has encouraged your institute to expand the National Eye Health project. What can you tell us about your plans in this area, not only in 1990 but in 1991, doctor?

Dr. KUPFER. In March 1989, we held a large meeting with 35 organizations, 65 participants who represent voluntary, scientific groups, government and pharmaceuticals. As a result of that meeting a number of recommendations were made and a number of actions taken. This past January, we had a planning committee meet which endorsed a number of additional activities.

They are as follows: We are in the process of developing a national survey to determine the public's knowledge, attitude, and practices concerning the two major disease that this program will initially focus on, diabetic retinopathy and glaucoma. We are targeting messages about these two diseases to patients with diabetes and blacks over the age of 50 who are at high risk for glaucoma. We are going to develop a partnership group among the participants who met with us last year. We are developing a clearing house for eye health education material. We are actively disseminating the results of two clinical trials, one in glaucoma and one in diabetes. In addition, we are developing plans for a national toll free telephone line and pilot testing this information avenue. Finally, we hope to become more involved in applied research that will give us additional information on glaucoma prevention and treatment as well as research that deals with the economic impacts of eye care. The program is developing very rapidly.

Mr. NATCHER. What is your current budget request for this education program?

Dr. KUPFER. It is about $2,800,000.

CATARACTS

Mr. NATCHER. Are there other prevention activities which are a priority for the institute?

Dr. KUPFER. Perhaps our biggest priority in terms of prevention is in the area of cataracts. In the United States, about 1,300,000 cataract operations are performed each year at a cost of $3,500,000,000 to the health care system. We estimate that if we could slow the development of cataract by 10 years we would reduce by 50 percent the number of people needing surgery each year. We have thus made a major commitment to the development of a medical therapy to slow the development of the cataracts.

We are also very much interested in education through the National Eye Health Education program as a way of prevention. If individuals, for instance, with diabetes and diabetic retinopathy would come for treatment at an appropriate time the ravages of diabetes on vision would me markedly decreased.

Mr. NATCHER. Dr. Kupfer, we want to thank you for your appearance before the committee at this time. This has been a good hearing, Doctor. It always is when you and your associates come in. I say that to you on the record. I appreciate it.

Mr. Conte, I yield to you.

Mr. CONTE. Doctor, a recent study from one of my favorite places, Johns Hopkins, linked cigarette smoking with cataracts. If the data holds up, it would have profound implications for public visual health. Each year, over 1,000,000 Americans have cataract surgery and over 1,250,000 people worldwide are blinded by cataracts. What is the significance of the Hopkins study? Are you looking at this possible link? Do you plan any follow-up studies? Are you also looking at other potential causes of cataracts?

Dr. KUPFER. Yes, sir. This study related smoking to the macular cataract, an opacity in the center of the lens. We are very excited about that finding. This is an association, but we don't yet know whether it represents actual cause and effect. However, we have two other studies which are looking at this same relationship and that information should be available in the next few months. One study is being done in Boston and another is being done in Italy.

We are very much interested in following up on this finding. If it does appear in these other two studies, then we will make a major effort to try to determine whether this is cause and effect.

Mr. CONTE. Are you looking at other potential causes of cataracts?

Dr. KUPFER. Yes, sir. We have completed three case-control studies which are specifically geared to look for cataract risk factors. We will be in a much better position in the next four or five months to follow up on potential risk factors for cataracts. This is a very high priority. We are hoping to hold a workshop next spring on the latest findings.

INTERNATIONAL ACTIVITIES

Mr. CONTE. Doctor, as you know eye diseases are rampant in other parts of the world. There is tremendous suffering from blindness as a direct result of insufficient care and lack of health education. Can you tell us what activities has your institute been in-

volved in abroad? Parasitic eye disease is especially prevalent in Asia and Africa. What advances have been made in this field?

Dr. KUPFER. Our major activity abroad has been in the research area. We have conducted a case-control study of cataracts in India. That has already been published. We have identified some risk factors which we are very much interested in seeing whether they are also present in the case control study from Italy and from the United States.

We conducted a study of cataracts in Tibet about a year ago because we had been told by a number of observers that cataracts were 10 times more prevalent in Tibet than in other parts of that part of the world like China. We wanted to see if this was true because if it was it would be a very important finding. Findings revealed that cataracts are a little more prevalent in Tibet but not 10 times greater. That put in perspective some of the possible risk factors such as ultraviolet radiation. We don't think that is as much of a factor as it might have appeared to be two years ago.

We are also very much interested in vitamin A deficiency and have concluded a study financed by the Ford Foundation in South India. That study showed that giving vitamin A in a very small amount once a week which was the equivalent to that taken in by a child having an adequate diet, not only prevented the development of eye disease from vitamin A deficiency but reduced significantly the death rate.

As such vitamin A seems not only to play a role in prevention of blindness but also prevention of death. This is a very important finding and substantiates other findings that have pointed in this direction. We are beginning to see the World Health Organization of the U.N. moving in the direction of distributing vitamin A in small amounts and trying to stimulate the development of vitamin A rich foods in many of these countries.

The last area has been to develop cost-effective processes for the delivery of eye care in the developing world.

RETINAL TRANSPLANTATION

Mr. CONTE. For the world can you tell us what progress has been made toward the understanding of structure and functions of the visual system and isn't it especially important to know something about how the visual system develops too? I am excited to hear about the new eye cell transplant technique for blindness. So far it has only been done on rats as I understand it. There is hope that someday we can actually do it on people. Can you tell us more about this and what are the prospects of developing this for humans? You can answer that for the record.

[The information follows:]

RETINAL TRANSPLANTATION

A number of NEI-supported laboratories are pursuing this important new line of investigation. To date, the key experimental results have been obtained using animals, principally rats. The results continue to demonstrate, often in dramatic fashion, the potential ability of transplanted retinal pigment epithelial cells to halt the photoreceptor degenerative process in the eyes of a special rat strain that exhibits an inherited form of retinal degeneration. However, many fundamental questions remain about this phenomenon. For example, it is not clear whether it is the transplanted cells themselves; release of some critical factor or substance; or some other

aspect of the operation that halts the degeneration process. It is important to establish the exact mechanism in order to determine the best treatment strategy for use in humans. The demonstration that retinal degeneration can be halted in this one rat strain will lead quickly to attempts to extend this general type of approach to other animal models of retinal degeneration. We know that eye surgeons have made at least one attempt to move tissue from the periphery to more affected central regions of the retina in the same eye of a patient with age-related macular degeneration. For the reasons outlined, however, we are still some time away from full-scale human trials of a "transplantation" treatment strategy.

DIABETIC RETINOPATHY

Mr. CONTE. In October your institute presented findings from the nationwide clinical trial looking at diabetic retinopathy. Diabetes is a major loss. Is there any good treatment or, better yet, preventative measures that would save the sight of tens of thousands of Americans? Can you tell us what the major findings were and how significant those findings were and are you doing anything to follow up on those findings?

Lastly, can you tell us for the record, what are some of the eye complications caused by AIDS? What studies have you got going that would improve treatment of these complications?

With that I will answer the roll call.

[The information follows:]

EYE COMPLICATIONS OF AIDS

Cytomegalovirus (CMV) retinitis is the most common intraocular opportunistic infection in patients with the acquired immune deficiency syndrome (AIDS). Estimates of the prevalence of CMV retinitis in AIDS patients have varied from 6 to 38 percent, with an overall estimate of approximately 20 percent. The agents currently available for the treatment of CMV retinitis are ganciclovir and foscarnet. The relative efficacy and safety of these two drugs for the treatment of CMV retinitis is unknown. Also unknown is the optimal time to implement drug therapy for CMV retinitis that is confined to the peripheral retina.

The objectives of the CMV Retinitis Trial: Foscarnet-Ganciclovir Component (CRT) are to: (1) evaluate the relative efficacy and safety of foscarnet and ganciclovir for the treatment of CMV retinitis in people with AIDS; (2) evaluate the effects of the treatments on survival; and (3) compare the relative benefits of immediate treatment versus deferral of treatment of disease confined to specific zones of the retina.

Two hundred and forty patients will be recruited and randomized to the treatment groups. All patients will be randomly assigned to foscarnet or ganciclovir therapy. Prior to randomization, patients will be assigned to one of two groups based on the location and extent of retinitis in the more severely involved eye. The first group includes patients with more sight threatening retinitis. These patients will receive immediate treatment with the randomly assigned drug. The second group includes patients with retinitis that is less sight threatening. These patients will be offered the option of participating in a randomized comparison of immediate treatment versus deferral of treatment with either drug. Alternatively, patients may choose to decide themselves whether to have immediate or deferred treatment and have only their drug treatment randomly assigned. Patients in the deferral groups will be offered drug treatment when and if their retinitis becomes more sight threatening.

Both drugs are administered in a two step fashion: 14 days of induction followed by lifetime maintenance at lower doses. If, after the induction period, a patient's retinitis continues to progress, at least one additional course of induction and maintenance with the study-assigned drug will be initiated under most circumstances. If the use of the study-assigned drug is terminated because of efficacy or safety consideration, patients will be treated with the other study drug if appropriate. Patients will be followed until they withdraw from the study, the study ends, or death occurs.

DOWNWARD NEGOTIATIONS OF NIH RESEARCH PROJECT GRANTS

Mr. EARLY. Dr. Raub, would you provide to the Committee, for each institute, for 1989 and 1990, the grants that had the largest percentage of downward negotiation, that is, the largest competing grant and the largest non-competing grant, the identification numbers, amount of the percentage reduction for 1989 and 1990, the amount of the grant and the amount for salaries in that specific grant.

Dr. RAUB. I will be pleased to.

[The information will be provided to the Committee.]

Mr. EARLY. I thought most of the downward negotiation in grants were across the board.

Dr. RAUB. As a matter of NIH policy we have encouraged the case-by-case look for the reasons Dr. Kupfer was saying. In some cases the institutes have determined there was in fact little difference so attempted to make across the board cuts but it is not something we encouraged them to do.

Mr. EARLY. I can understand that. I think the director should have that autonomy but I want an indication so I can find it. I have many other questions that I will submit for the record.

Dr. KUPFER. May I comment? Although there is case-by-case consideration on the whole, the average reduction is the same for most grants. It is just that we feel that we owe it to the grantee to look at research grants individually.

Mr. EARLY. We will be in brief recess.

[Recess.]

Mr. NATCHER. Back on the record. Again, Dr. Kupfer, we want to thank you for your appearance before the committee.

Doctor, I believe you are the senior director now as far as the institutes are concerned.

Dr. KUPFER. Yes, sir, I am.

Mr. NATCHER. Maybe you were here the first day when I told my story about the Time magazine cover. I would have no trouble, doctor, in naming five or six at the National Institutes of Health to go on that cover. It is the same in education.

I want to thank you, Doctor, for your appearance.

Dr. KUPFER. Thank you, sir.

[The following questions were submitted to be answered for the record and the justifications follow:]

DIABETES COLLABORATIVE ACTIVITIES

Mr. Roybal. What collaborative efforts are being undertaken between the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Eye Institute (NEI) in the area of diabetes and eye disease?

Dr. Kupfer. The NEI and NIDDK coordinate their efforts in the area of diabetes and eye disease. The staff at each institute collaborate in reviewing ongoing and proposed clinical research concerning diabetes and eye disease. For example, the head of NEI's clinical trials branch sits on the Data and Safety Monitoring Committee of the Diabetes Control and Complications Trial (the largest clinical trial in diabetes sponsored by the NIDDK).

Additional clinical trials designed to reduce the secondary complications of diabetes, including blindness, are in planning stages. Specifically, consideration is being given to a new clinical trial of aldose reductase inhibitors. These enzyme inhibitors offer great promise in preventing diabetic retinopathy and neuropathy. A symposium jointly sponsored by the National Eye Institute and the Juvenile Diabetes Foundation will be held on September 4 and 5, 1990 to review the scientific evidence concerning this and other possible treatments. The NIDDK has collaborated with the NEI in organizing this symposium and providing the scientific expertise necessary for a careful review of possible medical treatments to prevent the secondary complications of diabetes.

EYE DISEASES IN MINORITIES

Mr. Roybal. What research are you conducting in regards to eye disease and Hispanics and other minorities?

Dr. Kupfer. Diabetic retinopathy is among the most debilitating complications of diabetes and is the leading cause of adult blindness in the United States. The prevalence of diabetes is much higher among Mexican-Americans than in the general population. Currently, the NEI is supporting a study being conducted among Mexican-Americans residing in Starr County, Texas, to determine risk factors for the development and progression of diabetic retinopathy.

Mr. Roybal. Is there more of an incidence of a particular eye disease among minority groups?

Dr. Kupfer. Preliminary information from the NEI-supported Baltimore Eye Survey of the prevalence of eye disease among urban Americans age 40 and older indicates that, compared to whites, blacks in the study had higher rates of glaucoma at all ages and developed glaucoma at lower intraocular pressures. The prevalence of glaucoma in blacks was 4.7 percent compared to 1.7 percent in whites of the same age group and socioeconomic background. The prevalence of blindness was 1.6 for blacks and 0.89 for whites. Moreover, the incidence of glaucoma did not rise appreciably among whites until age 65, but the increase among blacks was earlier, beginning at age 40.

Data from a pilot study of glaucoma in a Caribbean black population indicate that 13 percent of the Island's black population over age 54 has glaucoma.

Based on limited data, the incidence of diabetes and diabetic retinopathy among the Native American Pima tribe is high. According to 1981 data, 50 percent of the Pimas over age 35 had diabetes and the prevalence of retinopathy increased from 3 percent among Pimas who were newly diagnosed to 47 percent among those who had diabetes for 10 or more years.

REFRACTIVE ERROR/NEARSIGHTEDNESS AND FARSIGHTEDNESS

Mr. Roybal. What is the status of research on the treatment of far and short sightedness beyond corrective lenses?

Dr. Kupfer. Glasses or contact lenses can safely and predictably correct the refractive error of most patients. Therefore, any surgical procedure should meet very high standards of safety, effectiveness, and predictability before it can be routinely recommended. Results from a multi-center clinical trial sponsored by the NEI have shown that radial keratotomy, a surgical procedure in which radial incisions are made in the cornea, can reduce nearsightedness with few complications. The main drawback of the procedure is the difficulty in predicting the visual outcome in individual patients. Twenty-eight percent of eyes operated on in the trial remained nearsighted and 17 percent of eyes became farsighted.

Mr. Roybal. Is there treatment of these two problems with lasers?

Dr. Kupfer. The development of surgical procedures for refractive error continues to be a major challenge in ophthalmology, and more than a dozen such procedures are currently in the developmental stage. Many of these experimental techniques use high energy lasers, such as the excimer laser, to produce the surgical incision.

Mr. Roybal. Is this treatment available to the public?

Dr. Kupfer. Despite the natural desire for normal visual function without dependence upon external devices, none of the present surgical procedures has gained widespread clinical acceptance. The procedures all suffer from a common problem: the unpredictable effects of the corneal wound healing process in determining refractive outcome.

Mr. Roybal. How safe is such a procedure?

Dr. Kupfer. Refractive surgery cannot fulfill its full promise until we gain a more fundamental knowledge of the biological and mechanical properties of the cornea. This past fall, the NEI convened a workshop, "Corneal Biomechanics and Wound Healing", bringing together cell biologists, biochemists, surgeons, engineers, and physicists to determine the state of our knowledge in this field and to identify areas of research that need stimulation.

COLOR BLINDNESS

Mr. Roybal. What causes color blindness?

Dr. Kupfer. While the perception of color involves complex activities of the eye and brain, the causes of congenital (from birth) defects of color vision are more simply explained. The retina at the back of the eye contains types of seeing elements called rods and cones. The rods are also responsible for night vision and operate under conditions of dim light. The cones are responsible for color vision and operate in daylight conditions. There are three types of cones: blue, green, and red, which act together to allow us to perceive a magnificent range of color, from deep indigo to blazing red.

The formation of each cone pigment is controlled by heredity. An abnormal gene may subtly alter or completely eliminate a specific pigment. An individual who has inherited an abnormal gene can have difficulty distinguishing certain shades, such as reds and greens.

Many people have color vision deficiencies that are not hereditary. For example, aging changes may produce color vision abnormalities. By far, the most common color defect accompanies the normal aging of the lens, as in cataracts. In a child, the lens inside the eye is crystal clear, but thereafter the lens gradually darkens, making it difficult for some older people to distinguish dark blues from dark greens, or dark grays.

Some medications may affect color vision. Changes in color vision may also accompany retinal or optic nerve disease. Therefore, if you suspect a color vision problem, especially if it appears suddenly, you should consult your ophthalmologist.

Mr. Roybal. Are you conducting research in this area?

Dr. Kupfer. Basic research on color vision supported by the NEI has provided new insights into the causes of inherited human color blindness. Molecular biological, biochemical, and psychophysical approaches have been used. Dr. Jeremy H. Nathans, an NEI grantee at the John Hopkins University, has conducted pioneering research over the last few years identifying the three different human genes for the visual pigments in photoreceptor cells of the retina. These pigments are activated by different wavelengths of light and so initiate the process of human color vision.

Dr. Nathans has now extended this fundamental research to an examination of the visual pigment genes in individuals with inherited color blindness. He reasoned that the visual pigments may be defective or altered in these individuals. This line of investigation has already produced some impressive results. For example, Dr. Nathans has studied twelve affected families with a history of blue cone monochromacy, an inherited disorder that is characterized by a loss of both red and green color vision. He found that a small region of the gene for the red and green visual pigments is missing in these individuals. Thus, the determination of the molecular basis of one type of inherited color blindness,

blue cone monochromacy, has now been achieved, and this approach can be used as a strategy for studying other inherited human color vision defects.

COLLABORATIVE PROJECTS

Mr. Roybal. Are you conducting collaborative projects with the National Institute on Aging?

Dr. Kupfer. The NEI has not co-funded projects with the National Institute of Aging (NIA), but we have been cooperating with them in the area of low vision and the elderly for several years. In 1986, the NEI and NIA co-sponsored a request for applications on low vision; we funded nine projects and the NIA funded two. We are both currently collaborating with the National Highway Transportation and Safety Administration on driving by the elderly.

EYE PROBLEMS IN THE ELDERLY

Mr. Roybal. Are you conducting any specific research on eye problems and the elderly?

Dr. Kupfer. Most of the blinding eye diseases are age-related including glaucoma, cataract, and age-related maculopathy. As such, it could be said that most of our research portfolio is directed at eye problems of the elderly. Although biomedical research is making great strides in preventing and treating eye diseases that affect our older citizens, many people inevitably experience irreversible losses in vision. The NEI has actively fostered research on low vision and its rehabilitation for many years, and the National Advisory Eye Council has recently recommended increasing the NEI's emphasis in this area. In the current cycle of NEI program planning, there will again be a separate planning panel to address the needs of rehabilitation research. We are particularly interested in fostering collaboration between the eye care, basic vision research, and rehabilitation communities to ensure that the research has clinical, scientific, and everyday validity. Topics of special interest include characterizing better the nature of residual vision in low vision patients, determining the visual requirements of everyday tasks, such as driving and reading, and assessing systematically new and existing vision aids.

The National Eye Health Education Prog am is also addressing the needs of older persons. It is especially important that elderly citizens, who are at increased risk for many of the blinding eye diseases, be aware of the need for regular eye examinations to detect abnormalities at a treatable stage.

REFRACTIVE ERROR

Mr. Stokes. How many people suffer from refractive problems?

Dr. Kupfer. More than 120 million Americans suffer from some type of refractive error, a developmental disorder in which the eye continues growth beyond the point where rays of light can be focused by the cornea and lens on the retina.

Mr. Stokes. What types of research is supported by NEI in the area of refractive problems (myopia, astigmatism, etc.) and at what level is it funded?

Dr. Kupfer. Over the past several years, scientists have determined, through the use of animal models, that eyes that receive blurred images or diffuse light experience this abnormal growth. Current research is investigating the biological mechanisms for this disorder. One very active line of research involves the process of accommodation, which is the change in the shape of the lens required to focus on near or far objects. It has been shown, for example, that the resting focus of the eye changes in the myopic direction after intense accommodative effort. Other research is looking at biochemical changes in the eye that accompany the development of myopia in animals. Epidemiological researchers are also beginning to study the changing relationships of the optical components of the eye during development of both normal and abnormal vision. Research on myopia, including surgical correction for the disorder, is funded at about $2.8 million per year. This amount includes support for 20 projects and one multicenter clinical trial, the Prospective Evaluation of Radial Keratotomy (PERK) study.

OUTREACH

Mr. Stokes. I understand that the purpose of the National Eye Health Education Program is to increase awareness among health care professionals and the public of scientifically-based health information that can be applied to preserving sight. The program focuses on the early detection and timely treatment for diabetic retinopathy and glaucoma. What is NEI doing to assure that optometrists and ophthalmologists are receiving information about diabetic eye research findings from NEI?

Dr. Kupfer. The NEI assures that both optometrists and ophthalmologists receive research findings through a variety of methods. For example, in the past year, NEI announced the results from the Early Treatment of Diabetic Retinopathy Study (ETDRS), an NEI-supported clinical trial. For this trial, NEI staff prepared a variety of information materials for both national distribution and distribution from participating clinical centers. Investigators from the trial were invited to meetings conducted by NEI staff about how to conduct publicity activities in their city that would mesh with national media activities.

NEI also developed and staffed an exhibit on the ETDRS study at the annual meetings of the American Academy of Ophthalmology and the American Academy of Optometry. Also, Institute staff wrote and distributed a fact sheet for patients that explained the study's

conclusions. To make certain that all ophthalmologists treating diabetic patients knew of the ETDRS conclusion, NEI prepared a clinical alert letter and worked with the American Academy of Ophthalmology to mail the alert to 22,000 ophthalmologists around the world. We have also been assisting the ETDRS investigators by providing editorial review and support for journal articles in preparation.

Distinguished representatives from the professions of ophthalmology and optometry are members of the National Eye Health Education Program (NEHEP) Planning Committee. That committee advises the Institute on the planning and development of program activities. Both the American Academy of Ophthalmology and the American Optometric Association will be invited to join the new NEHEP Partnership. Through the Partnership, comprising organizations interested in eye health education, the NEHEP will produce and disseminate state-of-the-art information as it becomes available. The NEI is also working closely with the American Academy of Ophthalmology in their Diabetes 2000 program aimed at educating ophthalmologists, primary care physicians, and allied health professionals about the important advances being made in the treatment of diabetic retinopathy.

NATIONAL EYE HEALTH EDUCATION PROGRAM

Mr. Stokes. Will there be other eye conditions that will be addressed? If so, what are they?

Dr. Kupfer. The initial focus of the National Eye Health Education Program (NEHEP) will be on the importance of early detection and treatment of diabetic retinopathy and glaucoma. These diseases were selected because of their high prevalence and the existence of important health messages concerning the importance of early detection and treatment in the prevention of blindness to be conveyed to a variety of target audiences. However, other topics, such as coping with low vision, will be incorporated into future NEHEP activities.

Mr. Stokes. What do you see as the greatest contribution the National Eye Health Education Program can make?

Dr. Kupfer. The ultimate goal of the NEHEP is to ensure that the results of eye and vision research are used for the benefit of all Americans. To achieve this goal, the NEHEP will develop effective information and education programs designed to reach those audiences at high risk for developing a specific eye disease, such as blacks over 50 at risk for developing glaucoma. These programs will disseminate messages that will help ensure that all individuals take advantage of early detection practices and receive prompt state-of-the-art treatment when appropriate. The NEHEP objectives are also in concert with the eye health objectives set forth by the Public Health Service's Office of Disease Prevention and Health Promotion in the Year 2000 Health Objectives for the Nation.

Mr. Stokes. Do outside organizations contribute to this education effort?

Dr. Kupfer. As part of its advisory structure, the NEHEP is developing the NEHEP Partnership. The purpose of the Partnership is to establish an ongoing, interactive relationship among the NEI and other key organizations that are concerned with eye health education or represent a specific target audience that can benefit from the NEHEP programs. The Partnership will provide members the opportunity to support the NEHEP through a variety of activities related to their own interests and capabilities. These activities may include the distribution of NEHEP materials, use of NEHEP messages and materials for local eye health education programs, participation on NEHEP task forces or other ad hoc groups, collaboration or co-sponsorship on specific eye health education activities, involvement in the evaluation of NEHEP materials, and exchange of information on related organizational activities with NEHEP. The NEHEP Partnership will be a network of strong, active organizations working together to turn scientific research findings into effective eye health education programs.

PARTICIPATION IN CLINICAL RESEARCH

Mr. Stokes. What is NEI doing to encourage optometrists and ophthalmologists to go into clinical research?

Dr. Kupfer. Encouragement of high-quality clinical vision research is a major goal of the NEI. In 1987, the NEI established the Collaborative Clinical Research Branch (CCRB) within the Extramural and Collaborative Program to promote and ensure the conduct of high quality clinical trials research. CCRB staff members have been guest speakers at meetings such as the American Academy of Optometry and the Association of University Professors of Ophthalmology where they presented information on the hallmarks of a successful clinical research application and funding mechanisms available to support clinical research. Vision researchers are encouraged to work closely with CCRB staff members as they design their clinical research studies and prepare grant applications for submission. This year will mark the eleventh annual course on "Clinical Vision Research" presented by the NEI at the annual meeting of the Association for Research in Vision and Ophthalmology. The primary goal of this course is to develop the skills of ophthalmologists and optometrists in planning and carrying out clinical studies. The NEI has a strong commitment to the promotion of clinical research activities by both optometrists and ophthalmologists.

Mr. Stokes. Are you actively recruiting through the Schools of Optometry and the Schools of Medicine?

Dr. Kupfer. Yes, the NEI is vigorously recruiting clinicians into vision research. This has been a continuing commitment on the part of the Institute. Schools of optometry and medicine are primary targets in this regard.

MYOPIA/NEARSIGHTEDNESS

Mr. Stokes. Your justification describes accommodation (the process by which the shape of the eye's lens changes to focus on objects at different distances) and its relationship to myopia (near-sightedness). Can you tell us about this relationship?

Dr. Kupfer. The relationship between accommodation and the development of myopia has been a controversial topic for many years. Myopia, or nearsightedness, occurs either if the optical power of the eye is too strong (refractive myopia), or if the eye itself is too long (axial myopia). In both types of myopia, the image comes to focus in front of the retina. Most myopia is of the second type which may progress rapidly, especially in the teen-age years, due to eyeball lengthening, and may require increasingly powerful corrective lenses. Occasionally, very extreme and rapidly developing myopia occurs that may cause retinal damage from excessive stretching of the retina and supporting tissues. Such rapidly progressing myopia is called "progressive," "malignant," or "pathological" myopia. Animal models of myopia are now beginning to shed some light on this issue. The relationship between accommodation and myopia is not clear in all animal models. However, studies suggest that axial growth is stimulated when the animal is required to accommodate for a substantial part of its daily behavior. There has been great interest in this clinically because of the possibility (as yet unproved) that intensive near work early in childhood could lead to myopia. Continued epidemiological as well as experimental research is needed to clarify the suggested relationship between myopia and accommodation.

Mr. Stokes. Do you have any evidence that intensive near work can lead to myopia?

Dr. Kupfer. Research on animals has shown that focusing on near objects for very extended periods results in an elongation of the eye during development. It has been claimed that a similar process may occur in young humans who spend many hours reading intensively and engaging in other types of close work activities. A recent review of the data on college age students by the National Research Council has given this problem new importance, since it has been found, for example, that many students who enter the Air Force Academy with perfect vision emerge sufficiently nearsighted four years later to disqualify them from flying.

MINORITIES' PARTICIPATION IN EYE RESEARCH

Mr. Stokes. What effort is the Institute making to increase the number of minorities involved in eye research?

Dr. Kupfer. The NEI is participating in the new NIH Initiatives for Underrepresented Minorities in Biomedical Research. We are providing administrative supplements to research grants for the support of underrepresented minority scientists and students. The aim of these programs is to attract and to encourage minority individuals to pursue careers in vision research. The NEI is currently supporting the research activities of seven such individuals through this program at a total cost of approximately $330,000.

The Institute also participates in the National Center for Research Resources' Minority High School Student Research Apprentice Program and its Minority Biomedical Research Support Program by funding specific projects within that program that are relevant to eye research.

The NEI plans to continue its Small Grant Program for Pilot Projects (R03). This program has as one of its specific "target populations" investigators at minority institutions.

The NEI is requesting that each organization applying for an institutional training grant provide their specific plans for the recruitment and retention of underrepresented minorities in their training program. Competitive renewal applications must document the results of these efforts during the previous funding period. This information is taken into consideration by the Initial Review Group, the National Advisory Eye Council, and the NEI staff in making funding recommendations.

The Intramural Program of the National Eye Institute has participated for many years in the minority summer student program conducted by the NIH Clinical Center Equal Employment Opportunity Office. This program identifies promising minority students, many in medical schools, and places them in research laboratories for the summer months to enable them to experience a research environment at a stage in their training when they are preparing to make definitive career choices.

In addition, the Intramural Program has a long history of supporting minority post-doctoral fellows who then go on to academic appointments. Traditionally, we have used the Staff Fellow Program to accomplish these goals. Currently, we have among the Staff Fellows two of Japanese descent, a Korean, a Latino, a Native American, and a naturalized Central African. In the new Intramural Research Training Associate Program, we currently have a Chinese physician in resident alien status, who intends to become naturalized. This program is targeted to American citizens and will be used more extensively in the future for minority recruitment.

RETINITIS PIGMENTOSA GENE

Mr. Early. I recently read about an exciting discovery by a group of eye scientists at the Mass Eye and Ear Infirmary who found the gene that causes blindness in children. Could you tell me more about this research?

Dr. Kupfer. Inherited retinal diseases such as retinitis pigmentosa (RP), which are characterized by a progressive loss of vision due to degeneration of photoreceptor cells of the retina are a major cause of blindness. They affect 100,000 Americans and 1.5 million people worldwide. The disease is usually diagnosed in childhood when the first symptom, night blindness, occurs. Recently, the gene for the autosomal dominant form of retinitis pigmentosa (ADRP) was localized to the long arm of human chromosome 3. This discovery and a previous finding that the gene for rhodopsin, an eye-specific protein, was mapped to this same region of the chromosome, prompted Drs. Thadeus P. Dryja and Eliot L. Berson, NEI grantees at the Massachusetts Eye and Ear Infirmary, to examine this particular gene in patients with ADRP. Using molecular biological techniques on DNA obtained from a large group of patients' blood samples, they discovered, in one form of ADRP, a mutation in the rhodopsin gene that corresponds to a specific amino acid substitution in the protein.

Mr. Early. Is it significant?

Dr. Kupfer. This is the first specific gene defect that has been described for any of the forms of retinitis pigmentosa. This significant scientific finding paves the way for identifying the role in photoreceptor degeneration and blindness of this defect in the gene for rhodopsin, a molecule that has been extensively studied by NEI grantees. Thus, there is already in place an extensive body of knowledge upon which this breakthrough can build.

CLINICAL TRIALS

Mr. Early. Will NEI fund any new clinical trials under the FY '91 budget request?

Dr. Kupfer. The Eye Institute will not initiate any new clinical trials under the fiscal year 1991 budget request.

Mr. Early. Are there any high priority clinical trials which are ready but cannot be initiated because of a lack of funds in the FY '91 request?

Dr. Kupfer. For fiscal year 1991, there are ten new clinical trials that are ready to be initiated.

Mr. Early. If so, please provide a list of these, along with a brief description and the associated costs, including first year costs.

Dr. Kupfer. A list of high priority clinical trials and the associated estimated cost follows:

MAJOR NEW CLINICAL TRIALS READY TO BEGIN IN FY 1991 IF FUNDS WERE AVAILABLE

(Dollars in thousands)

(NON-AIDS)

Title and Description	Estimated First Year Cost	Total Projected Cost
Therapeutic Oxygen in Retinopathy of Prematurity Previous case studies and animal model data demonstrate that chronic hypoxia during the retinopathy of prematurity (ROP) healing process may be a critical factor in differentiating ROP that progresses from ROP that regresses. These data justify the testing of the hypothesis that supplemental oxygen treatment will result in a reduction by at least one third in the number of infants with one or two eyes progressing to threshold (ROP). In this study, infants who develop pre-threshold ROP will receive continuous transcutaneous oxygen saturation monitoring and be randomly assigned to oxygen administration at one of two specified oxygen levels. ROP status will be determined prospectively. The outcome variable will be the number of infants who progress to threshold ROP for cryotherapy by three months after their expected date of full-term delivery.	$1,000	$5,400
Advanced Retinopathy of Prematurity Study The main objective of this multicenter, randomized clinical trial is to develop the best management strategy for children who fail cryotherapy. The study will assess efficacy of scleral buckling surgery for stage 4A and Stage 4B retinopathy of prematurity (ROP).	3,000	16,300
Contact Lens Evaluation in Keratoconus Keratoconus is a inherited cone-shaped, malformation of the cornea that causes visual impairment. The proposed clinical trial will examine the effects of two different contact lens fitting methods: a flat fitting method where the contact lens touches the corneal apex, and a steep fitting	1,000	5,400

Title and Description (con't.)	Estimated First Year Cost	Total Projected Cost
method where the contact lens clears the corneal apex. The randomized clinical trial would compare the safety and efficacy of the two fitting methods in keratoconus.		
Long-term Follow Up of PERK Patients The long-term follow up of patients from the Prospective Evaluation of Radial Keratotomy (PERK) study will provide information on the status of the cornea at various time intervals following this surgery. With this long-term follow up, any problems caused by radial keratotomy will be observed and any necessary intervention performed.	$500	$2,700
Quality of Life Assessment Following Glaucoma Treatment Utilizing a clinical trial design, eligible patients with newly-diagnosed open-angle glaucoma will be randomized to standard medication therapy or to immediate filtration surgery to reduce intraocular pressure. The primary outcome measures will be functional status and life satisfaction as measured in these two groups.	1,000	5,400
Treatment of Congenital Esotropia This would be a two-arm study in the treatment of congenital esotropia (crossed eyes). Arm-1 would have two phases. Phase-I would establish preliminary data on the dosage of the drug Oculinum, its effectiveness, and side effects in patients with angles of ocular deviation between 30° and 50°. Phase-II would consist of randomization of patients into a clinical trial of Oculinum versus surgical treatment if Phase-I shows that a randomized trial is feasible. Arm-2 would be a clinical trial of patients with more than 50° of congenital esotropia randomized into a standard two-muscle surgery approach versus a three- or four-muscle surgery approach. Arm-2 will be conducted independently of Arm-1.	4,000	21,700

Title and Description (con't.)	Estimated First Year Cost	Total Projected Cost
Efficacy of IOP Lowering in Ocular Hypertension This randomizes trial would determine whether lowering intraocular pressure by medical treatment prevents or delays the onset of glaucomatous optic disc and visual field damage in ocular hypertensive subjects who are judged to be at moderate risk for developing open-angle glaucoma.	$5,000	$27,100
Effect of Light Reduction on Retinopathy of Prematurity There is limited evidence to suggest that the intensity of light in the modern neonatal nursery may be one of the contributing factors to retinopathy of prematurity (ROP). The proposed randomized clinical trial will examine whether reducing light exposure of the eyes of prematurely born infants will prevent or reduce the incidence of moderate ROP. If light reduction is proven to be beneficial in reducing the incidence of moderate ROP, then a practical technique of light attenuation will be developed.	2,000	10,800
Barbados Glaucoma Treatment Trial The objective is compare the effectiveness of immediate filtering surgery versus conventional medical treatment in reducing visual loss in newly diagnosed black patients with open-angle glaucoma. Patients would be assigned randomly to either filtering surgery or to usual medical treatment and would be followed to ascertain visual function outcome.	1,000	5,400
Total Estimated Costs, Non-AIDS	18,500	100,200

National Eye Institute

MAJOR NEW CLINICAL TRIALS READY TO BEGIN IN FY 1991 IF FUNDS WERE AVAILABLE

(Dollars in thousands)

(AIDS)

Title and Description	Estimated First Year Cost	Total Projected Cost
CMV Retinitis Risk Factor A prospective cohort study to investigate the development and treatment of CMV retinitis in people with AIDS by identifying risk factors for the development of CMV retinitis in newly-diagnosed AIDS patients.	$3,100	$24,500
Total, AIDS	3,100	24,500
Grand Total, Non-AIDS/AIDS	21,600	124,700

CLINICAL TRIAL PLANNING GRANT

Mr. Early. I understand that NEI has designed a new grant mechanism, the NEI Clinical Trial Planning Grant. Why did NEI feel it necessary to establish this new grant?

Dr. Kupfer. Investigators submitting clinical trial applications for consideration by the NEI are encouraged to provide detailed information regarding the rationale, experimental design, protocols and procedure, analytical techniques, facilities and environment, adequacy of the proposed administrative procedures, and collaborative arrangements for the trial. Experience has indicated that this information is best provided in a well-documented Manual of Procedures (MOP) that is submitted as part of the application. However, preparation of the MOP can be time-consuming and costly. The NEI Clinical Trial Planning Grant provides a mechanism for early peer review of the rationale and need for the trial as well as support for the development of a detailed Manual of Procedures (MOP).

Mr. Early. What do you hope to accomplish?

Dr. Kupfer. First, early peer review of the rationale for the proposed clinical trial provides the investigator with an understanding of whether a full application for project support should be pursued. Second, the clinical trial planning grant provides investigators support for expenses incurred in the preparation of the detailed Manual of Procedures. As such, we think that this new grant mechanism will lead to the development of high quality clinical trial applications and will make more efficient use of personnel and resources.

Mr. Early. How will this grant be awarded?

Dr. Kupfer. An approved application will be considered for one year of funding at up to $50,000 in direct costs. Examples of the allowed uses of these funds include: paying travel expenses of clinicians, biostatisticians, epidemiologists, and other essential personnel who assist in the preparation of the MOP; supporting preliminary studies to refine trial procedures and document recruitment potential; paying for secretarial assistance and office supplies; and providing consultant fees for biostatisticians (but not generally for other scientific personnel).

RESEARCH MANPOWER

Mr. Early. Doctor, how would you assess the adequacy of research manpower in the fields of particular concern to your institute?

Dr. Kupfer. The NEI currently supports a large number of clinical trials and other epidemiologic research projects. These include single-center and multicenter randomized clinical trials, natural history studies, and risk factor analyses using case-control and prospective cohort methods. These projects all have the goal of improving the understanding, the prevention, and the management of visual system disorders. Yet, there is still an important need for a larger number of clinical vision research groups to participate and to provide leadership in the design, coordination, and conduct of such projects. This is a particular area of concern and we will be developing new initiatives to address this need.

CLINICAL VISION RESEARCH DEVELOPMENT AWARD

Mr. Early. Dr. Kupfer, how much is being allocated in FY '90 and FY '91 for the Clinical Vision Research Development Initiative, and how many awards do you expect to make?

Dr. Kupfer. No specific amount is set aside in a given fiscal year for the Clinical Vision Research Development Award. Since the program was started in FY 1988, six awards have been made: two in FY 1988, two in FY 1989, and two in FY 1990. Based on this history, I would project that the NEI would also make approximately two such awards in FY 1991.

RESEARCH OPHTHALMOLOGISTS RECRUITMENT

Mr. Early. Do you have difficulty recruiting research ophthalmologists? Why?

Dr. Kupfer. In the area of clinical trials and epidemiology, we are seeing a slow but steady increase in the participation of clinicians. However, we are still having difficulty recruiting and retaining clinicians at the interface between basic and clinical science. The long years of training required to be competitive and the relatively low salaries for research activities are disincentives.

CENTERS/CORE GRANTS

Mr. Early. Will research centers also be subject to downward negotiations in FY '90 and FY '91?

Dr. Kupfer. Yes, center awards will be cut in fiscal year 1990 and in 1991 as well.

Mr. Early. By what amount (percent) will competing centers be cut?

Dr. Kupfer. Competing centers will be cut by about 30 percent in fiscal years 1990 and 1991.

Mr. Early. By what amount (percent) will noncompeting centers be cut?

Dr. Kupfer. Noncompeting centers are subject to a 30 percent cut in both fiscal year 1990 and 1991.

Mr. Early. I see in the justification that the Institute will fund one new center in FY '91. What kind of center will be added?

Dr. Kupfer. The fiscal year 1991 budget request provides support for 30 center core grants, the same number as is currently being funded. We funded 29 center core grants in FY 1989. The new center in FY 1990 was recommended highly by the Initial Review Group and by the National Advisory Eye Council. The center will support shared resources and facilities for investigators who have achieved independent NEI funding for their individual research projects. These projects include studies of myopia, molecular and cellular neuroscience, and the possible use of perfluorocarbons in the interoperative management of retinal detachment.

Mr. Early. Why are you planning to add another center when faced with significant downward negotiation in the centers program?

Dr. Kupfer. No new center core grants would be funded in fiscal year 1991.

AWARD RATE

Mr. Early. What percentage of approved grants would be funded under the FY '91 budget request and how does this compare to FY '90 and FY '89?

Dr. Kupfer. The fiscal year 1991 budget request will allow the Eye Institute to fund about 38 percent of its approved grant applications. In fiscal years 1990 and 1989, the award rate is 42 percent and 47 percent respectively. As such, the award rate for fiscal year 1991 is about 4 percent less than the 1990 level and about nine percent less than the 1989 level.

Mr. Early. Doctor, do you think this is a good level, or do scientific opportunities warrant a higher level?

Dr. Kupfer. The decline in the percent of approved grants that the NEI has funded has made it somewhat difficult for the

vision research community to take full advantage of the many research opportunities that currently exist. We believe that there are still many high quality applications addressing important areas of research that cannot be funded at current levels.

DOWNWARD NEGOTIATIONS

Mr. Early. Have these downward negotiations in grants created any problems for your institute's researchers?

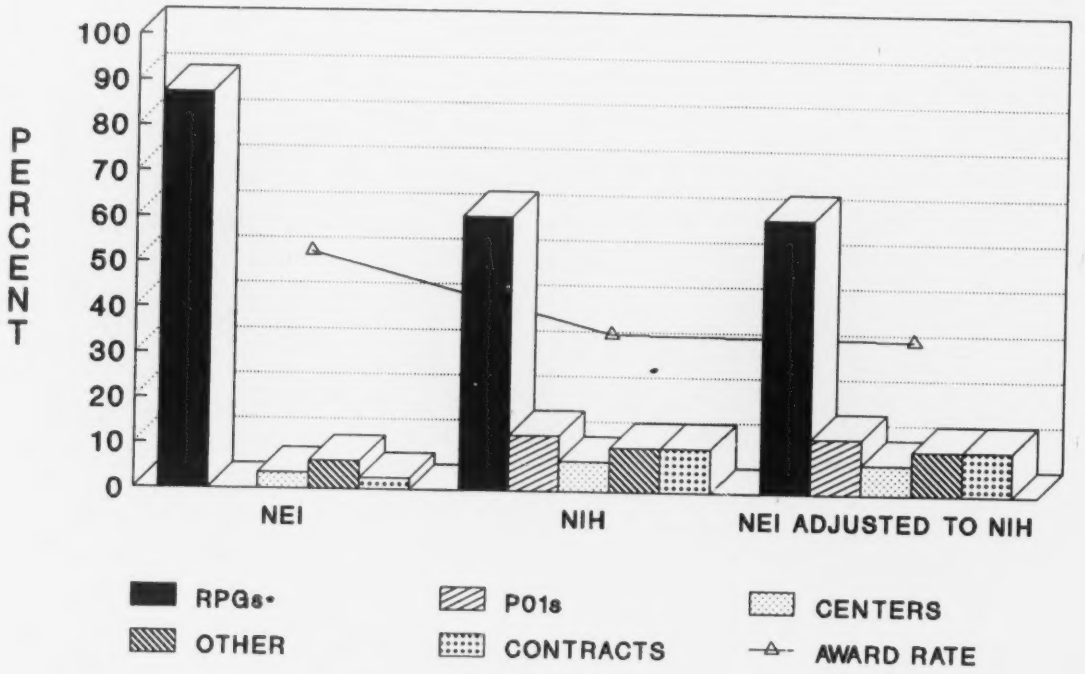
Dr. Kupfer. Cuts in research grants have created some problems for the investigators that the NEI supports. For multicenter clinical trials and other fixed-protocol clinical studies there is very little, if any, budget flexibility at the recommended level of support. For these projects, significant budget reductions mean that the pace of patient recruitment efforts, data analyses, and other vital activities will be slowed. For basic research projects, the situation varies for different research projects. For some investigators, significant reductions may simply mean that the overall pace of research will be slowed. However, many other investigators will have to choose carefully among the several approved specific aims of their research projects to determine which lines of investigation can proceed and which must be curtailed or, perhaps, eliminated. These can be difficult decisions.

AWARD RATE

Mr. Early. How does NEI support such a high award rate in FY '90 (42% as compared to the 24% for NIH as a whole) when it received the second lowest budget increase for an institute, about 2.3%?

Dr. Kupfer. The NEI's higher award rate for research project grants is a direct result of the Institute's deliberate and long-standing policy of making individual, investigator-initiated research project grants its principal support mechanism. And, within the research project grants category of awards, the NEI supports a very different mix of award mechanisms from many of the other NIH funding components. For example, the NEI does not support any program projects or any other type of large, umbrella-type awards such as multi-project center awards. One must take care, then, in trying to compare the NEI's relatively high award rate, based largely on traditional research projects (R01s) and first independent research support and transition awards (R29s), with that of other NIH components which are using these large umbrella-type mechanisms to a significant extent. It is really an "apples and oranges" comparison. Further, the NEI funds very few research and development contracts. An NEI staff analysis has demonstrated that if the NEI were to use these various mechanisms in the same proportion as the other institutes, its award rate would be nearly identical to the NIH average. (See Figure 1.) In short, by funding mostly R01 and R29 grants, the NEI is able to keep its average grant costs low (they are the lowest at NIH) and, therefore, the NEI is able to fund additional grants.

COMPARISON OF NEI AND NIH AWARD RATES FOR FY 1989



*R01,R23,R29,R37,R43,R44,U01(w/o P01)

Figure 1

NATIONAL EYE HEALTH EDUCATION PROGRAM

Mr Early. How many FTEs do you have for the National Eye Health Education Program in FY '90?

Dr. Kupfer. Three FTEs are assigned to the National Eye Health Education Program in fiscal year 1990.

Mr. Early. How many are included in your FY '91 budget request?

Dr. Kupfer. The fiscal year 1991 budget request includes four FTEs for the National Eye Health Education Program.

PROGRAM PLANNING FUNDING RECOMMENDATIONS

Mr. Early. To what extent does your FY '91 budget request reflect the recommendations of the NEI's Program Plan for 1990-1992?

Dr. Kupfer. In the 1987-1988 Biennial Report of the National Institutes of Health--Reports of the Advisory Councils and Boards, the National Advisory Eye Council (NAEC) developed a funding proposal for FY 1990 and 1991 to carry out the recommendations contained in the 1987 Evaluation and Update of the National Plan that were still deemed to be current, as well as to enable the Institute to pursue the new directions summarized in the Biennial Report. Although the funding levels recommended by the Council have not been achieved, progress has been and continues to be made toward satisfying the recommendations set forth in these documents.

USE OF ADDITIONAL FUNDS

Mr. Early. If an increase over the FY '91 budget request is provided, how would you use these additional funds?

Dr. Kupfer. There are a number of opportunities in improved health care and quality of life improvements that can be realized through further advances in molecular genetics, cell biology, and neuroscience [Decade of the Brain and related] research. To capitalize on these opportunities, the National Eye Institute would invest increased funds as follows:

- Restore funding for research project grants
- Fund the new clinical trials previously identified
- Strengthen support for centers
- Increase minority participation in biomedical research
- Provide support for construction
- Enhance support for research trainees

LOST OPPORTUNITIES

Mr. Early. Will any significant new research initiatives or opportunities be lost or delayed by lack of funds in the FY '91 budget request?

Dr. Kupfer. Yes, a number of significant improvements in health care and enhanced quality of life would be delayed as a result of lost opportunities in biomedical research.

Mr. Early. Please provide, for the record, a list of these along with a brief description and the funding requirements associated with each.

Dr. Kupfer. Significant opportunities would be delayed and/or lost that have the potential to further improvements in health care and the quality of life. Among them are:

- Further identification and characterization of the genetic defects that lead to retinal cell regeneration so that gene therapy or some other biologic method can be developed to intervene in such diseases as retinitis pigmentosa and macular degeneration.

- Work on using the polymerase chain reaction, a major advance in molecular genetics that facilitates the identification of genes. Using this technique, NEI-supported researchers could further work on the development of gene probes to study the effect of growth factors in the development of the visual nervous system and on the creation of transgenic animal models for genetic eye diseases.

- Additional work on strategies to encourage regeneration of damaged optic nerve tissue.

- More research on experimental retinal cell transplantation to determine whether the transplanted cells are functionally, as well as structurally, viable thereby enabling the animal to see.

- Increased research to examine how retinal cell proteins can be modified before transplantation to prevent their provoking an immune response that will cause graft rejection.

- Further elucidation of how the brain processes color and luminance information in parallel but separate pathways will significantly clarify how the brain is organized as a whole. Further work in this area could lead to the development of diagnostic tests for amblyopia and glaucoma.

- Progress in understanding how special proteins in nerve cells help maintain regenerative capacity could yield valuable information on how activity can modify brain function and repair nerves damaged by trauma.

- Determination of whether early surgery might be a better treatment than medication for newly-diagnosed open-angle glaucoma in terms of improved visual outcome and quality of life.

- Further research on determining how alterations in the lens epithelium lead to initial cataractous changes and determining if some metabolic event can be altered to prevent and/or slow early development of cataract.

- To capitalize on the potential benefits of the excimer laser in correcting refractive errors and corneal scars, a clearer understanding is needed of the cornea in terms of the fundamental biologic processes that control development and function, the biomechanics, and the mechanisms of wound healing.

In my professional judgement, these lost and/or delayed opportunities, translate into the following fiscal year 1991 costs:

	Associated Funding Requirements (Dollars in Thousands)
Extramural Research:	
Retinal and choroidal diseases	$113,674
Anterior segment diseases	83,328
Corneal diseases ..	(39,081)
Cataract	(21,249)
Glaucoma	(22,998)
Strabismus, amblyopia, and visual processing.	51,738
Laboratory renovation, instrumentation, and construction	10,000
Subtotal, extramural research	258,740
Intramural laboratory, clinical research, biometry and epidemiology	25,294
Research management and program services	9,516
Total, (Non-AIDS)	293,550

FUNDS TRANSFERRED

Mr. Early. It is my understanding that a portion of the NIH appropriation was transferred to the Agency for Health Care Policy and Research for health care services research. Was NEI money transferred?

Dr. Kupfer. Yes, each of the NIH institutes, centers, and

divisions are providing support for the Agency for Health Care Policy and Research.

Mr. Early. How much?

Dr. Kupfer. The Eye Institute's portion of the $28 million NIH tap the Agency for Health Care Policy and Research is $905,000.

HEALTH SERVICES RESEARCH

Mr. Early. Does NEI support its own health services research? Please highlight some examples of health services research supported by the NEI.

Dr. Kupfer. The NEI is currently funding 22 extramural clinical trials designed to evaluate the effectiveness of specific therapies for the treatment of a variety of eye diseases and disorders. These trials are: the Ocular Complications of HIV/AIDS Study, the Age-Related Eye Diseases Study, the Central Vein Occlusion Study, the Collaborative Ocular Melanoma Study, the Cryotherapy for Retinopathy of Prematurity Study, the Early Treatment Diabetic Retinopathy Study, the Macular Photocoagulation Study, the Silicone Study, the Sorbinil Retinopathy Trial, the Studies of Retinitis Pigmentosa and Allied Diseases, the Clinical Trial of Beta-Carotene and Macular Degeneration, the Prospective Study of Diabetes Control and Retinopathy, the Clinical Trial of Eye Prophylaxis in the Newborn, the Collaborative Corneal Transplantation Study, the Herpetic Eye Disease Study, the Prospective Evaluation of Radial Keratotomy Study, the Randomized Trial of Aspirin and Cataracts in U.S. Physicians Study, the Advanced Glaucoma Intervention Study, the Fluorouracil Filtering Surgery Study, the Glaucoma Laser Trial, the Optic Neuritis Treatment Trial, and the Prism Adaptation Study.

The NEI is also supporting a study to analyze the patterns of use of topically applied beta-blockers for the treatment of glaucoma in a population of over 1 million patients in New Jersey. This study will use computer-assisted investigation of a dataset containing all recipients in the New Jersey Medicaid program and the Pharmacy Assistance for the Aged and Disabled program. Another study is testing the hypothesis that the implementation of treatments based upon clinical trials in diabetic retinopathy, retinopathy of prematurity, and glaucoma, benefit not only the patient but also result in significant societal savings.

Recognizing the need to gather comprehensive, well-documented statistics on the incidence, prevalence, and costs of vision disorders in order to evaluate the effectiveness of clinical trials, the NEI supported two contract studies to determine the extent and costs of eye disorders and blindness in the United States. In these studies the total economic cost of visual disorders and blindness in 1981 was estimated to be about $14.8 billion. The NEI is also supporting an assessment of the relative costs of treatment as a part of the Collaborative Ocular Melanoma Study, a clinical trial designed to determine which of two standard treatments--enucleation or irradiation--prolongs the survival of patients with medium size choroidal melanoma.

HEALTH SERVICES RESEARCH

Mr. Early. Are there opportunities for health services research that the NEI could support in the future?

Dr. Kupfer. The NEI held a workshop in September 1988 entitled "Quality of Life With Visual Impairment" in order to discuss the incorporation of quality of life measures or health status assessments in NEI-supported clinical studies. As a result of that meeting, the Age-Related Eye Diseases Study, which was recently funded by the Institute, will determine whether existing instruments for measuring quality of life or health status can be used or new ones will need to be developed to assess the quality of life or health status of individuals participating in this study. The National Eye Health Education Program will also assess the extent and nature of public and professional knowledge of eye care and eye disease to assist in identifying the subjects on which to focus eye health information and activities.

RESEARCH SPACE

Mr. Early. As far as I can tell, all of the other institutes created before NEI's establishment have a definitive research facility for their intramural program. Does NIH have any plans for a discrete building for the NEI?

Dr. Kupfer. NIH has no plans at this time for a discrete vision research building.

Mr. Early. Is your research space adequate?

Dr. Kupfer. A number of NEI intramural research studies require highly specialized facilities for such operations as DNA sequencing, development of transgenic animal models, and studies of molecular genetics of specific viruses that can destroy the visual system. In 1986, NEI asked the NIH Associate Director for Research Services to allocate 12,000 additional square feet of research space. The space was needed for several reasons: to house existing research programs that were being displaced by the demolition of building 9, to relieve already overcrowded laboratories, and to provide space for new research initiatives. In response to this request, the NEI was granted 6,000 square feet of space. This space is projected to be available in 1992. It is also important to note that to correct its deteriorated primate space NEI will be given replacement space and about 1,500 additional square feet in primate holding space in the Child Health/Neuroscience Building. This increased primate holding space will allow NEI to further meet animal facilities and holding accreditation requirements including the provision to provide for the primates' psychological well being. While the space being provided will permit NEI to begin to relieve a long-term overcrowding problem and to improve animal holding, additional laboratory space is required to capitalize on the health care and quality of life improvement opportunities that are possible through enhanced research in molecular genetics, cell biology, and neuroscience. In addition, increased space would permit nongovernment organizations that have expressed a keen interest in providing training fellowships in NEI's intramural research program

to take advantage of this national resource.

Unfortunately, there are no plans to increase the Eye Institute's clinical research space. In fact, when Building 49 is occupied, it is projected that NEI will lose 1,300 square feet of clinical research space needed for its neuroophthalmology program in the NIH clinical center. Finally, the long-range plans of the NEI to consolidate all of its laboratory and clinical research in one facility is not being actively considered in NIH facility planning at this time.

TREATMENT ADVANCES

Mr. Early. What recent advances have there been in new drugs for the treatment of eye disease and disorders?

Dr. Kupfer. The drug 5-fluorouracil was tested in a multicenter, randomized clinical trial to determine if postoperative subconjunctival injections would increase the success rate of glaucoma filtering surgery in patients with clinically poor prognoses. The success rate after one year follow up in the 5-fluorouracil group was 80% compared to 60% in the standard treatment group. The results from this clinical trial were widely disseminated late last year. An extended follow-up study of all patients in the study is planned.

Investigators at Harvard Medical School have discovered that the combination of a well-known steroid hormone, hydrocortisone, and a molecule that helps to move small substances through biological membranes, beta-cyclodextrin, dramatically decreases neovascularization in animal models. Further research in animals may lead to clinical testing and application of this therapy in conditions such as diabetic retinopathy.

Para-amino-clonidine is a drug that has recently shown some promise in glaucoma therapy. It has been shown to be effective in lowering intraocular pressure in humans and at the same time does not have the systemic effects on blood pressure and heart rate so common to most glaucoma drugs. This drug may be of use in chronic glaucoma therapy. Considerable animal testing is necessary to learn the mode of action of this drug, how it is best administered, and learn what the side effects might be. The long-term efficacy of this particular pharmacological approach will have to be evaluated in long-term clinical studies.

The NEI has recently funded two new studies aimed at using a new muscle blocking strategy in the treatment of blepharospasm. Investigators at the University of Minnesota Medical School will determine if doxorubicin, an antibiotic known to have a toxic effect on muscles, can be successfully used as a permanent treatment for blepharospasm. In a related study at the Smith-Kettlewell Institute in San Francisco, investigators will determine if ricin, a cell toxin, is effective in this regard. Both projects will be carried out in appropriate animal models initially and will be tested in controlled clinical trials if the preliminary studies are successful.

AGE-RELATED EYE DISEASES STUDY

Mr. Early. Doctor, your Institute is planning an Age-Related Eye Diseases Study (AREDS). Why is this study important?

Dr. Kupfer. The National Eye Institute has initiated the AREDS to obtain important new information on age-related macular degeneration and cataract. This is an important research priority for the vision community because so many people are affected by these two eye diseases; yet, we have insufficient evidence on how or why cataracts or macular degeneration develop and progress. Patients with minor to severe drusen (deposits beneath the macula) and minimal lens opacities will be enrolled in the AREDS and followed over a ten-year period. During the course of this natural history study, a randomized intervention trial of nutritional supplements or some other clinical interventions are planned. Information provided by the AREDS will include not only the major risks for the development and worsening of cataracts and macular degeneration but also the possible effectiveness of a protective clinical intervention. The AREDS is a major undertaking for the NEI, and we believe the study will provide unique and much needed information.

It is also expected that valuable information will be gathered in a sub-study of AREDS about how people with cataracts and age-related macular disease value the quality of life provided by their years of good vision.

IMPACT OF VISION ON SCHOOL PERFORMANCE

Mr. Early. I understand that poor performance in school is often related to an undiagnosed vision problem. What is NEI doing to address this problem?

Dr. Kupfer. The relationship between vision and reading has been of considerable interest to optometrists, ophthalmologists, and educational specialists over the years. The focus of this interest has been on the importance of basic visual functions (refractive error, eye movements, accommodation, vergence) and visual perceptual-motor development in the attainment of successful reading and in the remediation of reading disability. How and to what extent clinical dysfunctions in these visual skills result in deficient reading remains speculative and demands further research. There has also recently been a suggestion of an early visual system deficit (in the so-called transient system) that could disrupt higher level visual processing, such as visual search and reading, and that is related to attentional mechanisms. A great deal of fundamental research conducted by our Strabismus, Amblyopia, and Visual Processing Program addresses directly these visual functions that have been implicated in reading disorders. NEI staff are also working with the National Research Council to devise a multi-disciplinary project that will evaluate the role of visual factors in reading disorders.

NATIONAL EYE HEALTH EDUCATION PROGRAM

Mr. Dwyer. Last year, the Committee urged the NEI to develop an effective education and prevention program for glaucoma and diabetic retinopathy. The budget justification states that the NEI will be initiating a new National Eye Health Education Program (NEHEP). Will doctors of optometry and general ophthalmology be included in NEHEP in order to better monitor patients with diabetic retinopathy?

Dr. Kupfer. Doctors of optometry and general ophthalmology will participate in the NEHEP through membership in the NEHEP Partnership, a network of eye health related organizations. As members in the Partnership, these organizations and their membership will receive information and educational materials that can be used with their patients. This information dissemination will help to ensure that patients are receiving the most up-to-date early detection methods, treatment, and follow-up care for diabetic retinopathy.

In addition, as new information becomes available as a result of NEI-supported clinical trials and other applied research projects, the NEI will issue press releases to national and local media and clinical alert letters to individual eye care professionals in cooperation with their respective professional organizations. NEI staff will also develop and staff exhibits at the annual meetings of these organizations.

Mr. Dwyer. What types of educational programs will NEHEP conduct for the public at large?

Dr. Kupfer. The NEHEP will conduct public education programs for specific target audiences at high risk for diabetic retinopathy and/or glaucoma. In its initial phase, the NEHEP will simultaneously develop two public information and education programs on glaucoma and diabetic retinopathy.

The glaucoma education program will initially focus on reaching blacks over age 50. The program will be designed to increase awareness of the high risk of glaucoma among blacks; increase knowledge that early detection and treatment of glaucoma may reduce the risk of blindness; and encourage regular, comprehensive eye examinations. Meetings with representatives from the black community will be held to assist the NEHEP in identifying and developing effective educational materials and strategies to reach this population, e.g., through the involvement of community leaders and community-based organizations, voluntary and professional organizations, and the media.

NATIONAL EYE HEALTH EDUCATION PROGRAM TARGET AUDIENCE

Mr. Dwyer. Will the education campaign be initially targeted to any particular group?

Dr. Kupfer. The diabetic retinopathy program will initially focus on reaching people with diabetes, including those segments at particularly high risk, such as Hispanics and Native Americans. The objectives of the program will be: 1) to increase awareness of

the seriousness of diabetic retinopathy as a threat to vision; 2) to increase knowledge that early detection and treatment of diabetic retinopathy may reduce the risk of blindness; 3) to encourage annual, comprehensive eye examinations; and 4) to encourage patients diagnosed with diabetic retinopathy to comply with appropriate recommended treatment. A task force has been established to assist the NEHEP in developing an effective diabetic retinopathy education program. A variety of strategies incorporating families and friends, media, and voluntary and professional organizations will be used to reach this audience.

CATARACT SURGERY

Mr. Dwyer. As you know, Medicare Parts A and B spend a tremendous amount of money each year on cataract surgery. Are certain individuals more apt to develop cataracts than others?

Dr. Kupfer. Among individuals at high risk to develop cataracts are people with diabetes and those exposed to certain drugs, chemicals, or radiation. However, scientists have not yet identified which individuals are at highest risk to develop aging-related cataracts, the most common type. Natural history and other epidemiologic studies of groups that may be at high risk for cataract are currently underway. This work may give clues to risk factors for this disease.

Results were published recently from one such study funded by the National Eye Institute on the effects of ultraviolet (UV) light on the development of cataracts. The study demonstrated a weak association between increased UV beta exposure and increased risk for cataract reported for watermen on Maryland's Eastern Shore. Watermen with the highest levels of UV exposure had an increased risk of developing cortical cataract. However, quantification of long-term sunlight exposure is technically difficult, and additional research will be needed to confirm this finding.

Mr. Dwyer. Are there any effective cataract prevention programs?

Dr. Kupfer. Because we do not yet know those factors that contribute to the formation of most cases of cataract, there are no cataract prevention programs. It is hoped that research eventually will identify risk factors that are associated with cataract development that will make possible cataract prevention programs in the future. In preparation for such programs, a cataract classification system has been developed for use in case-control studies of cataract development. It provides a reliable, reproducible system for clinical evaluation of lens opacities in nuclear, subcapsular, and cortical cataracts. This system will also be useful for assessing the effectiveness of anti-cataract drugs as they are developed. The National Eye Institute's cataract research program is almost exclusively devoted to prevention-related basic and clinical studies.

LASER TREATMENT

Mr. Dwyer. How many ophthalmologists utilize lasers to remove cataracts versus traditional surgical techniques?

Dr. Kupfer. Lasers are not used to remove cataracts. However, a non-coagulating laser is often used following cataract extraction to break apart the back part of the lens capsule left in place intentionally during cataract surgery if it later becomes cloudy and interferes with vision. This happens in about 40 percent of cases six months to 5 years after surgical cataract removal. We know of no data on how many ophthalmologists perform this procedure.

CATARACT SURGERY

Mr. Dwyer. What efforts are underway to minimize or alleviate complications and negative outcomes of cataract surgery?

Dr. Kupfer. There are few complications associated with modern cataract surgery. The use of preoperative evaluations and reliable surgical techniques for cataract surgery has led to this procedure being performed widely and successfully with very little risk. Yet, complications do occur in a few cases. Among those that contribute to a negative surgical outcome are retinal detachment and cystoid macular edema. Research supported by the NEI and other public and private funding sources is aimed at learning how better to prevent and treat such complications.

With data available from a new study of the effectiveness of cataract surgery funded by the Agency for Health Care Policy and Research, it will be possible to evaluate the effects of eye conditions such as glaucoma and retinal degenerations on the outcome of cataract surgery. Also, researchers will be analyzing data on the quality of life of patients following cataract surgery.

Mr. Dwyer. Are there any viable and effective alternatives to surgery?

Dr. Kupfer. Surgery is currently the only effective way to remove a cataract. The successful use of drugs to inhibit the formation of diabetic cataracts in an animal model has suggested that medical therapy to prevent or slow the development of diabetic cataracts in man may be possible. Studies are also underway of the role of anti-oxidants and other chemical agents in the possible prevention and treatment of aging-related cataracts.

The National Eye Institute's cataract research program is aimed ultimately at finding alternatives to cataract surgery through basic research into the mechanisms of lens transparency or opacification, clinical and epidemiological research into patterns of cataract formation in humans, and development of methods for the prevention and non-surgical treatment of cataract.

INTERNATIONAL ACTIVITIES

Mr. Dwyer. Onchocerciasis, more commonly known as River Blindness, is a terribly debilitating disease, afflicting tens of millions of people in Africa and to lesser extent in South America. The Merck pharmaceutical company, which is located in Rahway, New Jersey, has been donating Mectizan (Ivermectin) a very effective treatment of River Blindness for distribution in Onchocerciasis Control Plan areas. To what degree is the NEI working with the

Agency for International Development and the World Health Organization to combat River Blindness?

Dr. Kupfer. As part of its mission, the National Eye Institute is taking an active role in several broad-based international studies for the prevention, diagnosis, and treatment of blinding eye disease. The Institute supported the World Health Organization in conducting a major survey of the causes of blindness, among them onchocerciasis in Gambia. An NEI grantee is currently working in Venezuela in collaboration with the World Health Organization Center for the Prevention of Blindness on the role of the immune response to the disease with regard to human ocular pathology.

Mr. Dwyer. Has the NEI been working with the health authorities in Africa and South America on River Blindness and other eye disorders?

Dr. Kupfer. Several NEI grantees are involved in research concerning onchocerciasis, one of the four eye diseases considered the most devastating by the World Health Organization. In collaboration with local health authorities, a study is under way involving 600 subjects from Liberia and Sierra Leone, collecting and analyzing specimens. Intramural scientists are performing immunological and histopathological studies on ocular biopsy material from patients with onchocerciasis and from controls living in the same geographical area. Investigators in our extramural program are working on the development of an animal model of the human disease. Work is also underway on physiological studies to find new drugs to combat onchocerciasis.

GLAUCOMA

Mr. Hoyer. Open angle glaucoma is one of the leading causes of blindness among older americans and african-americans of all ages. The Baltimore Eye Survey revealed startling data about the incidence, prevalence, and severity of the disease, especially in African-Americans. Has the NEI established any particular goals or strategies that will develop research directions for the treatment of this disease?

Dr. Kupfer. It has been suspected for some time that the African-American population is at increased risk for glaucoma. The finding of the Baltimore Eye Survey of a two-fold excess prevalence of blindness and visual impairment from all causes in blacks when compared to whites provides further evidence suggesting an increased risk of glaucoma.

Our strategy has been to approach this problem both through research and through education. On the research front, the NEI is currently funding the Barbados Eye Study. This study is designed: to measure the prevalence of glaucoma and its associated visual impairment in a predominantly black population; to evaluate its risk factors; and to obtain the data necessary to prevent or control visual loss. The NEI is also funding a number of studies aimed at understanding the basic mechanisms involved in the pathology of the disease.

In the area of education, glaucoma is one of the two diseases being addressed by the National Eye Health Education Program (NEHEP). The glaucoma education program will initially focus on reaching blacks over the age of 50 who are at the highest risk for developing glaucoma. The objectives of this program will be: 1) to increase awareness of the higher risk of glaucoma; 2) to increase knowledge that early detection and treatment of glaucoma may reduce the risk of blindness; and 3) encourage regular, comprehensive eye examinations. The program will reach blacks through a variety of strategies that include involvement of community leaders and community-based organizations, voluntary and professional organizations, and the media. We also believe that the NEHEP will be effective in addressing the need identified in the Baltimore Eye Survey for receiving adequate correction for refractive error through the development of an education campaign to encourage regular, comprehensive eye examinations.

ACCESS TO EYE HEALTH CARE

Mr. Hoyer. What can you tell us about the access that different categories of Americans have to adequate eye health care at the "low" end where vision problems can be corrected with lenses as well as the "high" end where more intensive preventive or treatment measures are necessary?

Dr. Kupfer. The Baltimore Eye Study has also provided the startling information that the vision of 50 percent of those involved in the study could be improved, often dramatically, simply by providing them with the proper eyeglasses. This strongly suggests that a significant portion of at least the urban U.S. population does not have the benefit of even the most basic eye

care services. How much this reflects lack of access to care, a need for better eye health education, or both is not known, but clearly there are major unmet needs in this area. The existence of problems at the high end are suggested by findings from a Wisconsin epidemiologic study suggesting that nearly one-third of those who could benefit from laser treatment for advanced diabetic retinopathy do not have this treatment. There are no doubt various reasons for this--and in some populations access is clearly a major problem. However, it is also evident that lack of awareness of the seriousness of the problem and misconceptions about the nature of laser treatment are key factors as well. It is these knowledge gaps that NEI's National Eye Health Education program will be addressing directly in its targeting of diabetes patients and their families.

FEMALE PARTICIPATION IN CLINICAL TRIALS

Mr. Hoyer. To what extent are women as subjects involved in the clinical trials supported by the NEI?

Dr. Kupfer. The NEI currently supports 21 randomized, controlled clinical trials. None of these trials exclude women as participants, unless they are pregnant at the time of the eligibility examination and significant additional risks to the health of the pregnant woman or the fetus would be encountered in following the study protocol. In actuality, women account for roughly half the patients enrolled in our clinical trials.

Mr. Hoyer. Could you outline the NEI policy that is intended to assure adequate representation of women in the trials and how it is enforced?

Dr. Kupfer. Given that most of the eye diseases under investigation in our clinical trials are chronic diseases that specifically affect both sexes equally, the scientific design of these studies ensure that women are eligible participants. The peer review group reviewing the scientific merit and design of a study and NEI staff take care to see that the eligibility criteria are appropriate for the condition under investigation. No award is made until all appropriate eligibility criteria are included in the study design. After an award is made, an independent Data and Safety Monitoring Committee monitors the progress of the study to ensure patient safety and adherence to study patient eligibility criteria and protocol. An NEI staff member serves on each of these committees.

Mr. Hoyer. Can you provide the committee with a comparison of the number of women involved in each trial conducted over the past three years?

Dr. Kupfer. Each clinical trial supported by the NEI includes women as participants and no trial specifically excludes women from participation. Examples of the percentage of women participating in some of our trials follow:

Advanced Glaucoma Intervention Study: 53% women, 47% men
Central Vein Occlusion Study: 45% women, 55% men
Glaucoma Laser Trial: 56% women, 44% men

Corneal Transplantation Study: 44% women, 56% men
Ocular Melanoma Study: 52% women; 48% men

AIDS RESEARCH

Mr. Hoyer. There are ophthalmic disorders that are commonly associated with AIDS. To what extent is the NEI AIDS program focused on the opportunistic infections that accompany AIDS as compared to the HIV infection itself?

Dr. Kupfer. Of the opportunistic infections that threaten the sight of AIDS patients, cytomegalovirus (CMV) retinitis is the most common. In 15 to 45 percent of AIDS patients, CMV progressively destroys the retina, causing severe visual impairment and blindness.

NEI is supporting and conducting research in this area both extramurally and intramurally. The objectives of the NEI-supported, extramural CMV Retinitis Trial (Foscarnet Ganciclovir Component) are to: (1) evaluate the relative efficacy and safety of foscarnet and ganciclovir for the treatment of cytomegalovirus (CMV) retinitis in people with AIDS; (2) evaluate the effects of the treatments on survival; and (3) compare the relative benefits of immediate treatment versus deferral of treatment of disease confined to zones 2 and 3 of the retina.

Two-hundred forty patients will be recruited and randomized to the treatment groups. All patients will be randomly assigned to foscarnet or ganciclovir therapy. Prior to randomization, patients will be assigned to one of two strata based on the location and extent of retinitis in the more severely involved eye. The first strata includes patients with retinitis in zone 1 (posterior pole) or extensive retinitis in zones 2 and 3 (peripheral retina); these patients will receive immediate treatment with the randomly assigned drug. The second strata includes patients with retinitis that is confined to less than 25 percent of zones 2 and 3. These patients will be offered the option of participating in the comparison of immediate treatment versus deferral of treatment. Patients opting to participate in this comparison will be randomly assigned to immediate treatment versus deferral. Patients preferring to choose either of these options will have only their drug treatment randomly assigned. Patients in the deferral groups will be offered drug treatment when and if their retinitis becomes more sight threatening.

NEI intramural investigators in collaboration with NIAID are now conducting a study in which a group of CMV retinitis patients have been given either AZT or a combination of AZT and foscarnet. This is the first randomized controlled clinical trial for treating ocular complication of AIDS. Investigations of CMV progression or regression in this trial should help elucidate the nature of CMV retinitis in AIDS patients.

Mr. Hoyer. What do we know about the development and treatment of these infections that affect the vision of AIDS patients, for example don't these infections usually affect patients with more seriously compromised immune systems?

Dr. Kupfer. Two drugs have shown promise in reducing or halting visual loss in AIDS patients: ganciclovir, the only drug approved by the FDA for the treatment of CMV retinitis, and foscarnet, an investigational drug which has not been as widely studied as ganciclovir. NEI intramural scientists have found that ganciclovir when used alone is most effective against CMV retinitis at dosages that can cause dangerously high toxicity. Because ganciclovir and AZT, the only drug proven effective in prolonging life in AIDS patients, suppress bone marrow, they cannot be used together at the standard dosages. Foscarnet does not suppress bone marrow, so theoretically it could be used with AZT; however, foscarnet may cause kidney damage and must be discontinued when major kidney toxicity occurs.

AIDS patients may develop CMV retinitis at any stage in the progression of their disease. Typically, this infection will first appear in the peripheral retina, and, if not treated, will progress to the posterior retina as their disease progress.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

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NATIONAL INSTITUTES OF HEALTH

National Eye Institute

For carrying out section 301 and title IV of the Public Health Service Act with respect to eye diseases and visual disorders [$241,205,000] $247,392,000.

(Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 1990.)

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Amounts Available for Obligation 1/

	1989 Actual	1990 Appropriation	1991 Estimate
Appropriation.....	$234,218,000	$241,205,000	$247,392,000
Enacted administrative reduction.....	-2,988,000	-1,316,000	---
Sequester order.....	---	-3,356,000	---
Subtotal, adjusted appropriation.....	231,230,000	236,533,000	247,392,000
Real transfer to the Office of the Assistant Secretary for Health for AZT grants.....	-60,000	---	---
Comparative transfer to:			
Division of Research Resources, NIH for administrative cost of the RCMI program.....	-7,000	---	---
Fogarty International Center, NIH for passport activities.....	-4,000	-4,000	---
Comparative transfer from:			
Office of the Director, NIH for FTE increase.....	245,000	---	---
Subtotal, adjusted budget authority....	231,404,000	236,529,000	247,392,000
Unobligated balance lapsing.....	-171,000	---	---
Total obligations.....	231,233,000	236,529,000	247,392,000

1/ Excludes the following amounts for reimbursable activities carried out under this account: 1989 - $264,000; 1990 - $160,000; and 1991 - $160,000.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Budget Mechanism
(Dollars in Thousands)

	1989 Actual		1990 Appropriation		1991 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research grants:						
Research projects						
Noncompeting	836	$123,387	860	125,450	889	136,725
Admin. supplemental	(27)	1,704	(30)	1,213	(30)	1,253
Competing						
Renewals	190	31,078	131	24,628	111	22,046
New	116	13,770	110	13,659	102	12,997
Supplemental	4	227	6	342	5	272
Subtotal, competing	310	45,075	247	38,629	218	35,315
Subtotal, research projects	1,146	170,166	1,107	165,292	1,107	173,293
Research centers						
Core/specialized	29	7,019	30	6,613	30	6,613
Subtotal, centers	29	7,019	30	6,613	30	6,613
Other research						
Research career programs	25	1,616	24	1,813	24	1,813
Cooperative clinical research	29	7,846	38	13,380	38	13,420
Minority biomedical support		366		294		319
Other research related	62	2,594	64	2,299	64	2,299
Subtotal, other research	116	12,422	126	17,786	126	17,851
Total, research grants	1,291	189,607	1,263	189,691	1,263	197,757

Training						
Individual awards						
Noncompeting	43	1,105	48	1,344	32	928
Competing	34	800	38	1,077	54	1,488
Subtotal, individual awards	77	1,905	86	2,421	86	2,416
Institutional awards						
Noncompeting	174	4,165	123	3,444	73	2,044
Competing						
Renewal			26	728	54	1,609
New			19	517	41	1,036
Subtotal, institutional	174	4,165	168	4,689	168	4,689
Total, training	251	6,070	254	7,110	254	7,105
Research & development contracts	36	4,944	51	6,588	51	6,588
	FTEs		FTEs		FTEs	
Intramural research	152	22,375	156	23,615	161	26,256
Research management and support	60	8,408	68	9,006	68	9,686
Extramural construction 1/				519		
TOTAL	212	231,404	224	236,529	229	247,392
HIV/AIDS	(4)	(4,965)	(6)	(5,533)	(7)	(5,887)

1/ Includes approximately $519,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Crosswalk - 1989 Actual
(Dollars in thousands)

PROGRAM ACTIVITY	Mechanism: Research Grants — Research Projects	Research Grants — Research Centers	Research Grants — Other Research	Training Programs — Individual	Training Programs — Institutional	Research & Development Contracts	Intramural Research	Research Management & Support	Total
Retinal and choroidal diseases	$74,746	$5,806	$6,238	$913	$1,541	$4,655			$93,899
Anterior segment diseases	59,041	763	5,267	399	1,230	289			66,989
Strabismus, amblyopia and visual processing	36,379	450	917	593	1,394				39,733
Intramural research							$22,375		22,375
Research management and support								$8,408	8,408
TOTAL	170,166	7,019	12,422	1,905	4,165	4,944	22,375	8,408	231,404

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Crosswalk - 1990 Appropriation 1/
(Dollars in thousands)

PROGRAM ACTIVITY	Mechanism									
	Research Grants			Training Programs		Research & Development Contracts	Intramural Research	Research Management & Support	Extramural Construction	Total
	Research Projects	Research Centers	Other Research	Individual	Institutional					
Retinal and choroidal diseases	$70,643	$5,056	$11,205	$1,096	$1,396	$6,415				$95,811
Anterior segment diseases	57,934	514	5,634	733	1,428	173				66,416
Strabismus, amblyopia and visual processing	36,715	1,043	947	592	1,865					41,162
Intramural research							$23,615			23,615
Research management and support								$9,006		9,006
Extramural construction									519	519
TOTAL	165,292	6,613	17,786	2,421	4,689	6,588	23,615	9,006	519	236,529

1/ Includes approximately $519,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Crosswalk - 1991 Estimate
(Dollars in thousands)

PROGRAM ACTIVITY	Mechanism								
	Research Grants			Training Programs		Research & Development Contracts	Intramural Research	Research Management & Support	Total
	Research Projects	Research Centers	Other Research	Individual	Institutional				
Retinal and choroidal diseases	$74,062	$5,056	$11,270	$1,091	$1,396	$6,415			$99,290
Anterior segment diseases	60,739	514	5,634	733	1,428	173			69,221
Strabismus, amblyopia and visual processing	38,492	1,043	947	592	1,865				42,939
Intramural research							$26,256		26,256
Research management and support								$9,686	9,686
TOTAL	173,293	6,613	17,851	2,416	4,689	6,588	26,256	9,686	247,392

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Summary of Changes

1990	Estimated budget authority	$236,529,000
1991	Estimated budget authority	247,392,000
	Net change	+10,863,000

		1990 Current Estimate Base		Change from Base	
		Pos. (FTEs)	Budget Authority	Pos. (FTEs)	Budget Authority
Changes:					
A.	Built-in:				
1.	Within grade increase		$ 11,138,000		+142,000
2.	Annualization of January 1990 pay raise		11,138,000		+164,000
3.	One extra day of pay		11,138,000		+46,000
4.	January 1991 payraise		11,138,000		+682,000
5.	Federal Employees Compensation Fund		38,000		+2,000
6.	Unemployment compensation increase		18,000		+1,000
7.	FTS rate increase		180,000		+6,000
8.	Payment for centrally furnished services		8,628,000		+625,000
9.	Service and supply fund increase		3,273,000		+120,000
10.	Increased cost of laboratory materials and other supplies		12,855,000		+424,000
11.	DHHS Working Capital Fund		312,000		-16,000
	Subtotal				+2,196,000

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Summary of Changes-Cont'd

	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting.....	860	126,663,000	+29	+11,315,000
b. Competing.....	247	38,629,000	-29	-3,314,000
Total.....	1,107	165,292,000	0	+8,001,000
2. Other research.....		17,786,000		+65,000
3. Training.....		7,110,000		-5,000
	FTEs		FTEs	
4. Intramural research.....	156	16,721,000	+5	1,125,000
5. Extramural construction...		519,000		-519,000
Subtotal.....				+8,667,000
Total changes.....				+10,863,000

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Budget Authority By Activity
(Dollars in thousands)

	1989 Actual		1990 Appropriation 1/		1991 Estimate	
	FTEs	Amount	FTEs	Amount	FTEs	Amount
Retinal and choroidal diseases		$93,816		$95,811		$99,290
Anterior segment diseases		66,961		66,416		69,221
Strabismus, amblyopia and visual processing disorders		39,690		41,162		42,939
Intramural research	152	22,360	156	23,615	161	26,256
Research management and support	60	8,406	68	9,006	68	9,686
Extramural Construction				519		
Total obligations	212	231,233	224	236,529	229	247,392
Unobligated balance lapsing	--	+171	--	--	--	--
Total, budget authority	212	231,404	224	236,529	229	247,392
HIV/AIDS	(4)	(4,965)	(6)	(5,533)	(7)	(5,887)

1/ Includes approximately $519,000 to be transferred to other accounts for Extramural construction in accordance with Public Law 101-166.

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NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Budget Authority by Object

	1990 Appropriation	1991 Estimate	Increase or Decrease
Total number of full-time permanent positions.....	195	195	--
Total compensable workyears:			
Full-time employment.....	228	233	+5
Full-time equivalent of overtime and holiday hours.....	1	1	--
Average ES salary.....	$78,438	$96,310	+17,872
Average GM/GS grade.....	10.50	10.50	--
Average GM/GS salary.....	$37,046	$38,380	+1,334
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207).....	$65,961	$68,335	+2,374
Average salary of ungraded positions.....	$21,232	$21,996	+764
Personnel compensation:			
Full-time permanent.....	$6,175,000	$6,391,000	+216,000
Other than full-time permanent.....	2,668,000	2,854,000	+186,000
Other personnel compensation	325,000	354,000	+29,000
Special personnel service payments.....	490,000	524,000	+34,000
Total personnel compensation.....	9,658,000	10,123,000	+465,000

	1990 Appropriation	1991 Estimate	Increase or Decrease
Personnel benefits.....	1,480,000	1,591,000	+111,000
Benefits for former personnel	9,000	11,000	+2,000
Travel and transportation of persons.....	466,000	482,000	+16,000
Transportation of things.....	53,000	63,000	+10,000
Rent, communications, and utilities.....	493,000	511,000	+18,000
Printing and reproduction....	88,000	98,000	+10,000
Other services:			
Project contracts.....	6,588,000	6,588,000	--
Centrally furnished services.....	8,628,000	9,253,000	+625,000
Other.....	7,339,000	9,369,000	+2,030,000
Supplies and materials.....	2,753,000	2,887,000	+134,000
Equipment.....	1,654,000	1,554,000	-100,000
Grants, subsidies and contributions.....	197,320,000	204,862,000	+7,542,000
Total, budget authority ...	236,529,000	247,392,000	+10,863,000

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National Eye Institute

Significant Items In The House And Senate Appropriations Committee Report

Item	Action Taken or to be Taken
1990 House Report	
National Eye Health Education	
1. "The Committee is looking forward to full implementation of the National Eye Health Education Program (NEHEP) and encourages the Institute (NEI) to expand the glaucoma and diabetic retinopathy....Last year, when the Committee initiated this important program, positions for the NEHEP were added. The Committee notes that two positions have been assigned to this program, but the Institute's total staffing has declined from 217 FTEs in FY 1988 to 207 FTE's in FY 1990. Moreover, these positions were lost from the intramural program. It was not the Committee's intention to mount the NEHEP at the expense of ongoing research. The Committee's recommendation includes funds to support these FTEs and expects the NIH to provide administrative ceiling to add 2 research positions." (p.74-75)	1. The NEI is continuing to make progress toward full implementation of the National Eye Health Education Program (NEHEP). Recommendations from the NEHEP Planning Conference in March 1989, are currently being implemented. At that meeting, representatives from government and the private sector met to define and prioritize the education and information needs of the Program. These include establishing an advisory structure for the NEHEP which includes nurses, other health care professionals, and those organizations with an interest in eye health will guide program planning and development; preparing a strategic plan including specific activities for eye health education pertaining to glaucoma and diabetic retinopathy; sponsoring a national survey to assess the knowledge, attitudes, and health care practices of black people at risk for glaucoma and older people who have diabetes and may develop diabetic retinopathy; coordinating existing eye health education materials; and establishing a national, toll-free telephone information

Item	Action Taken or to be Taken
1990 House Report	
	service to provide a central resource for those needing information about eye health. With regard to staffing, in the 1990 appropriation, the House provided three additional FTEs to the NEI. In adherence to the intent of the Congress, the NEI distributed the FTEs as follows: two for the intramural research program and one for NEHEP.
Glaucoma and Diabetic Retinopathy	
2. "The Committee believes that blindness from both glaucoma and diabetic retinopathy can be greatly reduced in this Nation with an effective education and prevention program. Glaucoma is the leading disease causing blindness and is clearly preventable." (p.75)	2. In response to recent Congressional mandate, the NEI has begun to plan a new National Eye Health Education Program (NEHEP). The initial focus of the NEHEP will be public and professional education relating to the importance of early detection and treatment of diabetic retinopathy and open-angle glaucoma, the most common form. Diabetic retinopathy is the most common eye complication of diabetes, a disease that affects an estimated 11 million Americans. It is the leading cause of new cases of blindness in the U.S. among persons aged 20 to 74 years. Over the past 13 years, controlled clinical trials have demonstrated that various methods of laser treatment are highly effective in preventing visual loss from diabetic eye disease. Such treatment is now widely available throughout the United States. Yet, there is evidence that many people who could

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Item	Action Taken or to be Taken
1990 House Report	
	benefit from laser treatment do not have it, pointing out the importance of public and professional education for this disease. Open-angle glaucoma is the leading cause of blindness in older people and black Americans both young and old. Of the 2 million people known to have open-angle glaucoma, about 80,000 are legally blind. Although the disease itself cannot be prevented, it can be treated and blindness from the disease is almost always preventable. However, because open-angle glaucoma is usually asymptomatic in its early stages, millions of otherwise healthy people are unaware that they have the disease. Because early detection is the key to saving sight, those at risk for these diseases need regular, comprehensive eye examinations through dilated pupils. The NEHEP programs, now in development, will deliver this important health message to selected target audiences.

Item	Action Taken or to be Taken
1990 Senate Report	
Low Vision Research	
1. "The NEI was established to conduct and support research on eye diseases and blindness. Although such research has yielded advances that have improved the health and quality of life of thousands of people, many serious eye problems remain that in the aggregate pose an enormous burden in suffering an economic loss to our Nation. The Committee is aware of progress being made in low-vision research and encourages NEI to continue and expand its efforts in this regard." (p.141)	1. Low vision research has been accorded high priority within the programs of the National Eye Institute for several years. As a result, there is a growing cadre of experienced investigators who are now actively pursuing research in this area with NEI support. NEI staff have been involved in establishing the Low Vision Research Group which has its own electronic mail network, newsletter, and meeting. A committee of the National Advisory Eye Council has recommended the establishment of a separate program for Rehabilitation for Low Vision and Blindness within the Extramural and Collaborative Programs of the NEI. There will be a separate scientific panel for this research area as part of the current five-year planning activities of Council.
Retinal Transplantation	
2. "The Committee urges continued research in the use of retinal transplantations to reverse degenerative eye disease."(p.141)	2. Several additional laboratories have begun to pursue this important new line of investigation. Some investigators are reorienting their existing research programs and new investigators are being drawn into this area. The results continue to demonstrate, often in dramatic fashion, the potential ability of transplanted retinal cells to halt the photoreceptor degenerative process. The retina and the eye appear to be a nearly ideal experimental system for fundamental research on the regenerative capacity of the central nervous system.

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Item	Action Taken or to be Taken
1990 Senate Report	
Diabetic Retinopathy	
3. "The Committee urges high priority be given to prevention of diabetic retinopathy and treatment of those already afflicted." (p.141)	3. Research on diabetic retinopathy has been pursued rigorously by both NEI-supported extramural investigators and by NEI intramural scientists. Experiments using animal models of diabetic retinopathy have provided new support for the idea that inhibitors of an enzyme, aldose reductase, may prevent or diminish the ocular complications of diabetes. Investigators are also searching for other means to prevent the growth of new blood vessels on the surface of the retina. Laboratory studies in animals have indicated that a combination of hydrocortisone and beta cyclodextrin can inhibit this process. Cell biological studies of this type may lead to new methods to prevent or delay diabetic retinopathy.
National Eye Health Educational Program	
4. "The Committee is looking forward to full implementation of the National Eye Health Education Program (NEHEP) and encourages the Institute to expand the scientific knowledge of health promotion activities in glaucoma and diabetic retinopathy... The Committee strongly urges NEI to utilize knowledge and expertise by systematically ensuring that professional nurses are involved in its programs and activities." (p.142)	4. Recommendations from the NEHEP Planning Conference in March 1989, are currently being implemented. At that meeting, representatives from government and the private sector met to define and prioritize the education and information needs of the Program. These include establishing an advisory structure for the NEHEP which includes nurses, other health care professionals, and those organizations with an interest in eye health will guide program planning and development; preparing a strategic plan including specific activities for eye health education pertaining to glaucoma and diabetic

Item	Action Taken or to be Taken
1990 Senate Report	
	retinopathy; sponsoring a national survey to assess the knowledge, attitudes, and health care practices of black people at risk for glaucoma and older people who have diabetes and may develop diabetic retinopathy; coordinating existing eye health education materials; and establishing a national, toll-free telephone information service to provide a central resource for those needing information about eye health.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1990 Amount Authorized	1990 Estimate	1991 Amount Authorized	1991 Budget Estimate
Research and Investigation...	Section 301	42§241	Indefinite	$229,419,000	Indefinite	$240,287,000
National Eye Institute.....	Section 455	42§2851	Indefinite		Indefinite	
National Research Service Awards..	Section 487(d)	42§288	Such sums as necessary 1/	7,110,000	Authorizing legislation to be requested 1/	7,105,000
Total Budget Authority.....				236,529,000		247,392,000

1/ This training authority is shared with other research training programs of the National Institutes of Health, and the Alcohol, Drug Abuse, and Mental Health Administration.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Appropriations History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1981	$116,046,000	$117,635,000	$117,884,000	$117,983,000
1982	116,445,000 2/	132,920,000	133,014,000	127,374,000
1983	131,550,000	138,763,000	145,040,000	141,897,000
1984	142,333,000	149,600,000 3/	151,966,000 3/	152,262,000
1985	157,873,000	171,097,000 4/	187,181,000	178,591,000
1986	183,341,000	188,988,000 5/	184,036,000	195,094,000
1986 Sequester				-8,389,000
1987 6/	179,201,000	219,091,000	214,080,000	216,637,000
1988	184,829,000	234,382,000 7/	231,529,000	224,947,000
1989	229,021,000 8/	223,288,000 9/	229,271,000	234,218,000
1990	233,777,000 10/	240,636,000	241,774,000	239,889,000 11/
1990 Sequester				-3,356,000
1991	247,392,000			

1/ Reflects enacted supplementals, recissions, and reappropriations.
2/ Reflects the September amendment; the original request was $132,324,000.
3/ Excludes $3,585,000 in NRSA training programs not considered.
4/ Excludes $3,900,000 in NRSA training programs not considered.
5/ Excludes $5,231,000 in NRSA training programs not considered.
6/ The budget estimate to congress proposed that all funding for AIDS research be consolidated in the Office of the Assistant Secretary for Health. The House allowance consolidated all NIH AIDS funding in the Office of the Director, NIH; the Senate allowance and appropriation spread the funding among the Institutes, including $104,000 for the NEI.
7/ Proposed advanced appropriation to cover the continuation costs of competing research project grants awarded in 1988.

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8/ The 1989 request excludes funds for AIDS research and education ($4,947,000).
9/ Excludes $5,620,000 in NRSA training programs not considered.
10/ The 1990 request excludes funds for the National HIV program ($5,697,000) proposed for consolidation in the office of the Assistant Secretary for Health.
11/ Excludes enacted administrative reduction of $1,316,000.

Justification

National Eye Institute

	1990 Appropriation		1991 Estimate		Increase or Decrease	
	FTEs	BA	FTEs	BA	FTEs	BA
TOTAL....	224	$236,529,000	229	$247,392,000	+5	+$10,863,000
HIV/AIDS.	(6)	(5,533,000)	(7)	(5,887,000)	(+1)	(+354,000)

General Statement

Eye diseases and disorders reduce the quality of life of millions of Americans, taking an enormous physical, mental, social, and economic toll. An estimated 10 million Americans have irreversibly impaired vision. About half a million are blind. Approximately 40 percent of our Nation's 10 to 11 million diabetics suffer from diabetes-related eye problems. Nearly 2 million adult Americans have glaucoma. In economic terms, eye diseases and blindness cost the Nation about $16 billion annually.

As the Nation's primary resource for the conduct and support of eye and vision-related research, the National Eye Institute (NEI) fosters research aimed at improving the treatment, diagnosis, and prevention of eye diseases and disorders. Research is supported extramurally through the award of research grants, fellowships, training grants, and contracts to investigators at universities, medical schools, and other research institutions. In addition, to assess the benefits and risks of new or alternative treatments for eye diseases, the NEI funds clinical trials. Organizationally, these awards are made through six major programs: Retinal and Choroidal Diseases, Corneal Diseases, Cataract, Glaucoma, and Strabismus, Amblyopia and Visual Processing, and Cooperative Clinical Research.

The NEI also conducts research intramurally at its in-house laboratory and clinical facilities. Intramural researchers focus on eye disorders that are not extensively investigated by extramural scientists. These complementary programs permit the NEI to support effectively and efficiently a broad spectrum of eye and vision-related basic and clinical studies.

Over the years, a number of sight-saving health care advances have resulted from NEI's continued investment in vision research. Lasers have been effective for the treatment of some ocular complications of diabetes, as well as a variety of other eye diseases. New drugs are being tested for the

treatment of a number of eye diseases and disorders, including uveitis and ocular herpes infection. Uveitis alone is responsible for about 10 percent of all blindness and visual impairment in the United States. Treatment of the two million adult Americans who have glaucoma has changed significantly as a result of research on new medications. It is important to note that before these drugs were developed, surgery was the only effective treatment for the most common form of glaucoma. Improvements in preserving and storing donor corneas have mad corneal transplantation the most successful of all tissue transplant operations.

NEI intramural and extramural research investigators remain at the forefront of biomedical research, applying the latest techniques of immunology, biotechnology, cell biology and molecular biology to numerous sight threatening disorders. However, to maintain this edge, vision research must continue to attract, maintain, and train a cadre of individuals who can capitalize on the latest biomedical technologies at hand and develop those of tomorrow. This will aid in accomplishing our ultimate goal -- to improve the visual health of the nation.

In addition to NEI's continued emphasis on the conduct and support of eye research and research training, NEI has embarked on a national eye health education program using funds specifically appropriated by congress for this purpose. This program's goal is to provide a lifetime of good vision through improvement of health professionals' and the public's knowledge of vision impairment risk factors, with an emphasis on early diagnosis and treatment. The program will initially emphasize early detection and prompt treatment of glaucoma and diabetic retinopathy, two of the leading causes of blindness in the United States. Using a partnership approach, NEHEP works with a variety of public and private sector organizations interested in eye health education.

Overall Budget Policy

The 1991 budget request for the National Eye Institute favors basic research and totals $247,392,000, an increase of $10,863,000 over the comparable 1990 estimate. This amount includes $5,887,000 for AIDS, an increase of $354,000 over the 1990 funding level. With regard to research project grants, the request will support 1,107 awards, the same total number of projects as in 1990. The projected distribution is 889 noncompeting grants at $136,725,000 and 218 competing grants at $35,315,000. Also, approximately 254 trainees will be funded, the same number of trainees as will be supported in 1990.

In 1991, 30 core grants will be awarded, the same level as in 1990. The request includes $17,851,000 for the other research category, an increase of $65,000 over the 1990 level. This increase includes $25,000 for minority biomedical support and $40,000 for AIDS cooperative clinical research. All

other categories in this mechanism will be funded at the 1990 level including research careers.

For intramural research, the request includes $26,256,000, and $9,686,000 is requested for research management and support, an increase of $2,641,000 and $680,000 respectively. These funding levels include support for basic operating requirements including materials and supplies, personnel expenses, management fund, and animal care facilities.

Program Accomplishments

Neurobiology--Two separate research teams, working independently, have successfully transplanted normal rat retinal pigment epithelium (RPE) cells into the eyes of rats with an inherited retinal degeneration. The RPE cell layer acts as an interface between the photoreceptor cells of the neuronal retina and its blood supply. When the RPE cells fail to perform their function, cellular debris accumulates, causing photoreceptor degeneration with resulting loss of vision. In the rat model used in these studies, transplantation of healthy RPE cells abruptly halted degeneration. This research advance raises the possibility of cell replacement therapy for inherited blinding diseases like retinitis pigmentosa.

Intramural scientists have discovered that a group of neurons within the brain possess unique properties that may play a key role in integrating visual information with eye position and eye movements. We perceive a stable visual world in spite of the fact that visual images change their positions on our retina with each eye movement. Studying the neural mechanisms of visual perception at the time of and after eye movements, these scientists found neurons of the pulvinar nuclei (a brain area) that are more responsive to a visual stimulus just after an eye movement than at other times. They found other cells in this area that appear to be very responsive to visual stimuli when the eye is in a certain position but almost unresponsive in other eye positions. This research furthers understanding of the functional contribution of specific brain areas to normal visual perception and may contribute to improved ability to pinpoint brain damage that has resulted in visual and perceptual defects.

Human Genome--The crystallins are a group of proteins found in the eye's lens and other body tissues. Two features of the crystallins make them an important system for studies directed at understanding the structure, organization, expression, and evolution of gene families: (1) crystallins are "conserved proteins" in that their molecular sequence has remained relatively unchanged in species along the evolutionary scale; and (2) crystallins have different functions depending on where they are found within the body even though the same gene controls their expression at the different sites. In the lens, crystallins are structural proteins responsible for the lens transparency that is important for clear vision. In other body tissues, the crystallin gene may be expressed as metabolic enzymes. Within the past year, the gene encoding human alpha B-crystallin gene has been sequenced and mapped to chromosome 11. In other studies, the human alpha A-crystallin gene was found to contain a coding sequence with a mutation, a base pair deletion from the sequence found in other species in which the gene is expressed. This deletion has caused the sequence to become non-functional. The discovery of this "pseudo-exon" shows that part of a functional gene can become inactive and provides an example of the dynamic aspects of evolution.

Biotechnology--Using biotechnological techniques, researchers have recently found a new polymorphism (variation) in the gene controlling the interphotoreceptor-binding protein (IRBP). IRBP is an extracellular protein that is thought to transport retinoids and fatty acids during the visual cycle. Study of IRBP is of great importance because a malfunction in the transport of retinoids or fatty acids could be an underlying cause of ocular disease. The new IRBP gene polymorphism was discovered by scientists who are studying families with genetic eye diseases in which IRBP is suspected to play a role. The new polymorphism is, so far, unique to families with fundus albipunctatus, a rare, autosomal recessive disorder that causes a type of night blindness.

Scientists studying the retinoblastoma (RB) gene have provided direct evidence supporting a postulated mechanism of action of this gene and may have opened new avenues for cancer therapy. Retinoblastoma, an eye cancer affecting about 500 children each year in the U.S., is associated with loss or alteration of the RB gene. Therefore, it was thought that the RB gene acted to suppress tumor formation. In recent experiments designed to test this hypothesis, researchers have demonstrated that introduction of a cloned RB gene into cultured tumor cells significantly inhibited growth and suppressed tumorigenesis in mice. Replacement of suppressor genes in tumor cells, as demonstrated in these studies, point to the possible utility of gene therapy in treatment of some types of cancer.

Clinical Trials--The Fluorouracil Filtering Surgery Study (FFSS) is a multicenter, randomized clinical trial that began in September 1985. This trial was designed to determine whether postoperative subconjunctival injections of 5-fluorouracil (5-FU) would increase the success rate of glaucoma filtering surgery in patients with poor prognosis. 5-FU interferes with the growth of scar tissue that can later block the surgical opening. Filtering surgery, the creation of a drainage channel to relieve the buildup of intraocular pressure, is standard treatment to prevent blindness from uncontrolled glaucoma. Sometimes, however, scar tissue blocks the surgically created channel, necessitating a second surgery to reopen it. The study tested the effectiveness of 5-FU in preventing formation of scar tissue. Early results from this clinical trial show that one year after surgery, 73 percent of the patients who received 5-FU did not need reoperation but 50 percent of the patients who had standard surgery without 5-FU did. Results also show that 66 percent of the patients receiving 5-FU maintained satisfactory intraocular pressure without drugs, compared to only 36 percent of those who did not receive 5-FU. Moreover, the 5-FU patients who needed drugs for intraocular pressure control required fewer drugs than did those who had surgery alone. Extended followup of all patients participating in the FFSS is planned. The followup study will answer important clinical questions such as the long-term safety of 5-FU in high risk glaucoma patients.

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AIDS Research Program

Ophthalmic disorders are commonly associated with the acquired immunodeficiency syndrome (AIDS), and blindness is among the many terrible complications of this disease. Cytomegalovirus (CMV) retinitis is an opportunistic infection of the retina that occurs predominantly in more severely immunocompromised AIDS patients. It is a direct viral infection of the retina characterized by white infiltrates and hemorrhages. This ocular complication of AIDS can severely damage the retina and is the major cause of visual loss and blindness in AIDS patients. Unfortunately, little is known about the factors that may influence the development or prognosis of CMV retinitis. The NEI is supporting both basic and clinical research of the developmental mechanisms and treatment strategies of these opportunistic infections of the eye.

Recent Research Accomplishments

Through cooperative agreements, NEI is supporting a core group of investigators with expertise in AIDS, retinal diseases, clinical trial methodology, and epidemiology. The group's first priority has been to develop a clinical trial to investigate the risks and benefits of emerging strategies for CMV retinitis. Currently, the antiviral drug ganciclovir is the only drug licensed in the U.S. for the treatment of CMV retinitis. However, ganciclovir is most effective at dosages that frequently produce bone marrow suppression, as does AZT. Consequently, the two drugs cannot be used concurrently. Foscarnet, an investigational drug for CMV retinitis, has shown activity against the virus that causes AIDS as well as herpes viruses, including CMV. The major objectives of the clinical trial are to compare the relative safety and efficacy of foscarnet with that of ganciclovir for treating CMV retinitis and to evaluate their relative effects on patient survival in the treatment of CMV retinitis. In addition, a risk factor study protocol aimed at identifying risk factors for the development of CMV retinitis and at determining the prevalence and incidence of CMV retinitis in newly diagnosed AIDS patients has been developed. Training of clinical staff at the clinical centers and pilot testing of the clinical trial protocol began in mid-November 1989.

NEI intramural investigators in collaboration with NIAID are now conducting a study in which a group of CMV retinitis patients have been given either AZT or a combination of AZT and foscarnet. This is the first randomized controlled clinical trial for treating ocular complications of AIDS. Investigations of CMV progression or regression in this trial should help elucidate the nature of CMV retinitis in AIDS patients.

Research Plans

Eleven clinical centers, a coordinating center, and a fundus photography reading center are participating in the clinical trial of foscarnet and

ganciclovir and the risk factor study. It is planned to recruit approximately 240 AIDS patients with CMV retinitis in one or both eyes will be recruited over an 18-month period starting in March 1990. AIDS patients with sight-threatening and non-sight-threatening CMV retinitis will be included in the clinical trial. Patients with sight-threatening disease will be randomized to either foscarnet or ganciclovir treatment. Patients with non-sight-threatening disease will be randomized to receive either foscarnet treatment, ganciclovir treatment, or to deferral of treatment unless major progression occurs.

The NEI will continue to support a small number of investigator-initiated research projects grants for basic science related to AIDS.

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National Eye Institute

Retinal and Choroidal Diseases

Authorization: Indefinite.

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$95,811,000	$99,290,000	+$3,479,000

Purpose and Method of Operation

The retina is a delicate, multilayered tissue that lines the back of the eye. It converts light energy into neural signals and relays this visual message to the brain. A blood-vessel-rich tissue, the choroid nourishes the retina. Collectively, diseases and disorders of the retina or choroid are the leading cause of blindness in the United States. The most important of these include diabetic retinopathy, age-related macular degeneration, retinitis pigmentosa, retinal detachment, ocular inflammation (uveitis), cancers, and damage caused by toxic agents and drugs. Unfortunately, for most of these conditions, there is neither means of cure nor prevention. Progress against them depends on gaining new knowledge of the fundamental processes related to retinal and choroidal function and on developing new clinical approaches.

The NEI supports both clinical and fundamental scientific research related to retinal and choroidal disease. The latter provides basic information about the normal functioning of the retina and the choroid, the changes that occur in disease states, and the scientific basis for developing new modes of prevention, diagnosis, and treatment. Research is funded by grants and contracts, cooperative agreements, institutional training grants, and individual fellowships, with emphasis on basic research.

Rationale for the Budget Request

The 1991 budget request for the Retinal and Choroidal Diseases program is $99,290,000, an increase of $3,479,000 over the 1990 estimate. The 1991 request includes support for about the same number of projects as in 1990: 481 research project grants, 23 core grants, 48 grants in the other research category, and approximately 85 full-time-training positions.

Visual Cycle. Dr. Robert R. Rando and his colleagues at Harvard University have discovered an important metabolic step that is vital for the formation of the visual pigment, rhodopsin. Rhodopsin is the light-sensitive protein that initiates the conversion of light energy into visual signals in the retina. This new discovery resolves a major, unsolved problem that has prevented a more complete understanding of the "visual cycle." The compound, 11-cis retinal, is needed for formation of rhodopsin, but it is not a dietary constituent and therefore, must be synthesized by the body. The Harvard investigators have discovered that the synthesis 11-cis retinal takes place in the retinal pigmented epithelium cells of the eye and have defined the precise biochemical processes involved in this synthesis.

Molecular Genetics of Retinitis Pigmentosa. Inherited retinal diseases such as retinitis pigmentosa (RP), which are characterized by a progressive loss of vision due to the degeneration of photoreceptor cells of the retina, are a major cause of blindness that affects approximately 100,000 individuals in this country alone. Dr. Stephen P. Daiger at the University of Texas Health Sciences Center in Houston and colleagues in Scotland have been studying members of a large family with an autosomal dominant form of RP and have located the defective gene to a specific region on human chromosome 3. Two genes for eye-specific proteins have been assigned to this chromosomal location already, and they may be candidate genes for this form of the disease. These scientific findings pave the way for both identifying the defective gene and for carrier detection in this autosomal form of RP.

Retinal Transplantation. A year ago it was reported that Dr. James E. Turner and his colleagues at Bowman Gray School of Medicine, and, independently, investigators at Columbia University were able to transplant normal retinal pigmented epithelium (RPE) cells into the eyes of rats with an inherited retinal degeneration. The transplantation of these healthy cells abruptly halted the photoreceptor degenerative process. This line of investigation is being pursued vigorously in several additional laboratories. Recently, Drs. Martin S. Silverman and Stephen E. Hughes at the Central Institute of the Deaf in Saint Louis have successfully transplanted normal photoreceptor cells into the retinas of rats using novel techniques. The transplanted photoreceptor cells survive the surgical procedures for extended periods and appear to be metabolically active. Overall, these results demonstrate, in dramatic fashion, the potential ability of these transplanted cells to "rescue" or replace damaged or degenerating retinal cells.

Molecular Biology of Color Blindness. Dr. Jeremy H. Nathans, an NEI grantee at The John Hopkins University, has performed pioneering research in identifying visual pigment genes in both cone and rod photoreceptor cells. In addition, he has been using molecular biological approaches to study inherited color blindness in humans. Dr. Nathans has studied twelve affected families with blue cone monochromasy, a rare X-linked inherited disorder of color vision, and showed that a specific region of the DNA of the red and green visual pigments, components of the retina which are necessary for color

vision, is missing in these patients. Thus, understanding of the molecular basis of an inherited retinal disorder, blue cone monochromasy, has now been achieved which can guide studies of other inherited human color vision defects.

Retinoblastoma (RB). Retinoblastoma is an eye cancer which affects about 500 children each year in the United States. Research on RB has accelerated dramatically in recent years. As reported last year, the responsible, predisposing gene--which is either lost or has been altered--has been localized to chromosome 13, isolated, and characterized. Dr. Wen-Hwa Lee and his associates at the University of California, San Diego, have demonstrated that the introduction of the RB gene into tumor cells grown in culture can cause them to behave like normal cells. This exciting line of research has provided direct evidence for the postulated mechanism of action of the RB gene, which apparently suppresses the formation of the tumor and it may open up new avenues for cancer therapy. Dr. Lee has recently identified the protein product of the RB gene and has found that it binds to the cell's DNA, where it may normally act to suppress gene activity related to cell growth.

Retinopathy of Prematurity. Retinopathy of prematurity is a blinding retinal disease for which premature, low-birthweight infants are at high risk. In April 1988, the results of the Cryotherapy for Retinopathy of Prematurity clinical trial reported that the use of cryotherapy, a freezing technique, reduced the chances of further progression of the disease from 43% in untreated eyes to 21% in treated eyes. Long-term followup of these infants will be essential to evaluate the long-term safety and efficacy of the procedure. The NEI has recently funded a five-year follow-up study of the infants enrolled in this trial in order to attempt, for the first time, to correlate the structural changes observed in the different phases of retinopathy of prematurity with the eventual visual capabilities of the eye.

Age-Related Macular Degeneration. The National Advisory Eye Council, NEI's advisory body has encouraged the development of epidemiologic studies of age-related macular degeneration to ascertain risk factors for the disease and to obtain baseline data that will be needed for the design of prevention or treatment trials. The "Age-Related Eye Diseases Study" (AREDS) will enroll patients to follow the natural progression of this macular disease. The prospective nature of AREDS, its focus on the progression of the disease, and its evaluation of the effects of dietary factors make it a unique and much needed study. Ten participating clinical centers, a coordinating center and a reading center will be funded by contract this fiscal year.

National Eye Institute

Anterior Segment Diseases

Authorization: Indefinite.

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$66,416,000	$69,221,000	+$2,805,000

Purpose and Method of Operation

This program encompasses research on corneal diseases, cataracts, and glaucoma. The cornea is the transparent structure at the front of the eye that helps focus incoming light rays onto the retina. Because the cornea is exposed, it is particularly vulnerable to irritation or damage from trauma, infection, and toxic agents. If the lens, situated behind the cornea, becomes clouded with a cataract, the passage of light is obstructed and vision may be impaired. A cataract results from complex changes in the chemical composition of the lens that are not completely understood. Glaucoma can occur when the outflow of the fluid produced in the front chambers of the eye (aqueous humor) is impaired, leading to an excessive level of eye pressure. The increased pressure is often followed by gradual destruction of the optic nerve that can lead to visual impairment and blindness.

NEI-supported research on corneal diseases encompasses ocular infections and inflammatory diseases, ocular surface problems, refractive problems, corneal edema and dystrophies, and corneal transplantation and wound healing. Research on cataracts includes studies of how and why cataracts develop, ways to prevent cataracts or slow their progress, the safety and effectiveness of methods of treating cataracts, and better methods to correct vision after cataract extraction. Glaucoma research is directed at preventing blindness from glaucoma through studies of the optic nerve, eye fluid transport processes, improved methods for early detection and treatment, and epidemiological studies of the disease and its risk factors.

Research is funded by grants and contracts, cooperative agreements, institutional training grants, and individual fellowships.

Rationale for the Budget Request

The 1991 budget request for the Anterior Segment Diseases program is $69,221,000, an increase of $2,805,000 over the 1990 estimate. The 1991 request includes support for about the same number of projects as in 1990: 355 research project grants, 2 core grants, 58 grants in the other research category, and approximately 75 full-time-training positions.

Corneal Diseases

Approximately 4 million cases of corneal injuries and disorders are documented each year in this country. These problems, aside from refractive errors, necessitate about 10 million visits annually for professional eye care, or one third of all visits for medical or surgical eye treatment. Diseases of the cornea produce about 6 percent of all legal blindness in the United States, but are the leading cause of blindness worldwide. They are also, as a group, the most painful of eye disorders and account for considerable disability.

Control of Corneal Hydration. The normal cornea contains no blood vessels; it is nourished completely by the fluids that bathe it. The maintenance of corneal transparency depends critically on the tissue's ability to regulate its water content. Research on the molecular mechanisms of water transport adds to understanding of how edema or swelling, which characterizes a number corneal diseases, causes loss of corneal clarity. In the past year, Dr. Jorge Fischbarg at Columbia University has provided the first direct evidence that a membrane-bound protein known to transport glucose also functions as a channel for water transport. Specific inhibitors of glucose transport were shown to affect water transport. This finding may lead to the development of new drugs for the treatment of corneal edema.

Refractive Surgery. One hundred million Americans require correction of refractive error due to farsightedness, nearsightedness, or astigmatism. Traditionally, these problems are corrected with eyeglasses or contact lenses. Recently, ophthalmic surgeons have developed an array of new surgical techniques such as radial keratotomy, epikeratoplasty, lamellar keratoplasty, and keratomileusis to correct refractive errors by reshaping the corneal surface. The excimer laser is the latest development in the application of laser technology to ophthalmology. It destroys the chemical structure of biological tissue, rather than burn the tissue as other lasers do. It is claimed that the advantage of this instrument is that it can be precisely controlled to remove layers of the cornea with minimal scarring and with little damage to surrounding tissue. In achieving these technical advances, however, investigators have also found that they are limited by major gaps in knowledge of the fundamental biologic processes that control the development and function of the cornea, of corneal biomechanics, and of the mechanisms involved in corneal wound healing. Accordingly, the NEI has placed a high priority on stimulating fundamental research on the cornea.

Cataract

Many Americans develop cataracts, opaque areas in the normally clear lenses of their eyes, often in the sixth and seventh decade of life. More than 3 million people in the United States have some degree of visual impairment from cataracts. The surgical extraction of cataracts is one of the safest and most successful of all major operations. But, the operation is expensive, and unsatisfactory visual adjustments and complications do occur in a small percentage of cases. Accordingly, the NEI devotes most of its funding in this area to research aimed at the prevention or slowing of cataract development. Even modest delay of cataract formation could lead to significant reductions in the numbers of cataract operations performed.

Regulation of Lens Hydration. The transparency of the lens is controlled in part by the degree of hydration of its epithelial cells, fiber cells, and crystallin fibers. Recently, much work has focused on determining the molecular basis of fluid transport in the lens. Scientists have found that lens plasma membranes contain two distinct proteins that affect the movement of water. In the peripheral regions of the lens, a protein termed MP70 forms symmetric channels that can open or close to permit the passage of water molecules. In the central areas of the lens, the major protein of the plasma membrane, MIP, apparently minimizes the volume of extracellular space and protects the central lens fibers from swelling and clouding.

Crystallins. The crystallins are a group of proteins found in the eye's lens and other body tissues. Two features of the crystallins make them an important system for studies directed at understanding the structure, organization, expression, and evolution of gene families: (1) crystallins are "conserved proteins" in that their molecular sequence has remained relatively unchanged in species along the evolutionary scale; and (2) crystallins have different functions depending on where they are found within the body even though the same gene controls their expression at the different sites. In the lens, crystallins are structural proteins responsible for the lens transparency that is important for clear vision. In other body tissues, the crystallin gene may be expressed as metabolic enzymes. Within the past year, the human alpha B-crystallin gene has been sequenced and mapped to chromosome 11. In other studies, the human alpha A-crystallin gene was found to contain a base pair deletion from the coding sequence found in other species in which the gene is expressed. This mutation has caused the sequence to become nonfunctional. The discovery of this "pseudo-exon" shows that part of a functional gene can become inactive and provides an example of the dynamic aspects of evolution.

Development of a Cataract Classification System. The Lens Opacities Classification System (LOCS I) was developed for use in clinical studies of cataract. With the recently developed LOCS II System, scientists are able to grade lens opacities (nuclear, subcapsular, and cortical) by increasing severity and, therefore, can document cataract growth. An independent evaluation of the LOCS II system found excellent reproducibility when the LOCS II photographs were used for clinical or photographic cataract classification. The development of this new cataract classification system provides the first objective quantitative tool that could be used in prospective clinical studies.

Glaucoma

In glaucoma, visual function is lost due to progressive damage to the optic nerve. About 2 million Americans are known to have glaucoma, but surveys suggest that perhaps an additional 1 million individuals may have the disease yet are unaware of their condition.

Fluorouracil Filtering Surgery Study. This multicenter clinical trial has recently demonstrated a 50 percent improvement in control of glaucoma among patients at high risk for blindness. Open-angle glaucoma, the type studied and the most common form of the disease, is associated with aging and affects about 3 percent of people aged 70 and older. It is the second leading cause of blindness among all Americans and the leading cause among blacks. The disease is characterized by a rise in fluid pressure inside the eye, which damages the optic nerve. Most patients can control their glaucoma with medications, but when drops or pills fail, some patients need filtering surgery to provide a drainage outlet to lower the pressure. Sometimes, however, scar tissue blocks the surgical drainage channel, necessitating further surgery. This type of surgery is least successful in patients who have had a previous filtering surgery or who have had cataracts removed.

To determine whether injections of 5-fluorouracil, also called 5-FU, could enhance the success of filtering surgery, investigators from seven clinical centers recruited 213 high-risk glaucoma patients for the study. 5-FU impedes the growth of fibroblasts that can close the surgical opening. After the investigators performed the surgery and determined that the new drainage channel was working, the patients were randomized to receive 5-FU or to have no further treatment.

Randomization of patients into the study was stopped ahead of schedule when it became evident that the combination of surgery and 5-FU therapy was significantly superior to surgery alone. Of the 105 eyes treated with 5-FU, only 27 percent needed a second operation for control of intraocular pressure compared to 50 percent of the 108 eyes in the standard therapy group. Filtering surgery followed by injections of 5-FU provided an additional benefit. Two-thirds of the patients receiving treatment with 5-FU did not

need to resume taking medications to control their glaucoma. In the surgery alone group, only about one-third maintained satisfactory pressure without medication. Moreover, of those requiring medication after surgery, patients in the 5-FU group needed fewer types of drugs than those in the standard treatment group. Study Chairman Richard K. Parrish II, M.D., of the Bascom Palmer Eye Institute, University of Miami School of Medicine, said in announcing these results, "We will follow these patients for at least five years to determine whether the early results hold true. Now that we know 5-FU improves the short-term outcome for these patients, we can investigate whether lower doses of 5-FU or less rigorous injection schedules may produce the same or even better results."

Prostaglandins. The field of prostaglandin research continues to be important for glaucoma because it offers the potential for development of drugs that may be useful in the treatment of this disease. Prostaglandins are derivatives of naturally abundant compounds called lipids, which are found in tissues of animals and man. It was not until lower doses of highly specific prostaglandins called PGE and PGF were studied that their ocular pressure lowering properties were observed. Scientists are using organ culture of human donor eye tissue to determine exactly where these compounds exert their effect. Early results indicate that the ciliary muscle may be the site of action. Expansion or contraction of the ciliary muscle may influence ocular drainage of eye fluid by its mechanical action on neighboring drainage channels.

Glaucoma in Blacks. Glaucoma has been reported to be a much more aggressive disease in blacks compared to whites in the United States. Blacks are believed to have an earlier average age of onset of the disease, suffer blindness at a greater rate, and may be more resistant to treatment. The Baltimore Eye Survey has been able to quantify and compare the occurrence of glaucoma in 2,395 black and 2,913 white adult residents (aged 39 years and over) of East Baltimore. Preliminary results from this survey indicate that blacks have a higher prevalence of glaucoma in all age groups. The overall glaucoma prevalence in this study was found to be 4.7 percent among blacks and 1.7 percent among whites. The blindness rate was 15.5/1000 among blacks and 8.9/1000 among whites. Among individuals with glaucoma, blacks tend to develop glaucoma at lower ocular pressures compared to whites.

Caribbean blacks have also been reported to have a very high prevalence of glaucoma. In a pilot study in Barbados, 13 percent of blacks over the age of 54 were found to have glaucoma. The Barbados Eye Study was initiated to determine the prevalence of glaucoma in the black population of Barbados. The study will also seek information on risk factors for the early detection and treatment of glaucoma. In addition, the prevalence of cataracts, macular degeneration, and diabetic retinopathy will be examined in the population.

Sub Activities	1990 Estimate	1991 Estimate	Increase or Decrease
Cornea.....	$31,118,000	$32,438,000	+$1,320,000
Cataract.....	16,870,000	17,650,000	+780,000
Glaucoma.....	18,428,000	19,133,000	+705,000
Total Program....	66,416,000	69,221,000	+2,805,000

National Eye Institute

Strabismus, Amblyopia, and Visual Processing

Authorization: Indefinite.

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$41,162,000	$42,939,000	+$1,777,000

Purpose and Method of Operation

The Strabismus, Amblyopia, and Visual Processing program supports research directed toward gaining a better understanding of normal vision and the causes of visual deficits and blindness that do not result from specific dysfunction of the eye itself. This program supports research aimed at preventing or treating such disorders as strabismus (misalignment of the eyes), amblyopia (commonly known as "lazy eye"), myopia (nearsightedness), and neuro-ophthalmological disorders. Understanding visual processing and its disorders requires knowledge of the human nervous system, including molecular, genetic, chemical, cellular, and integrative processes that underlie perception and the control of eye movements.

Although disorders of visual processing may not always cause total blindness, they may seriously diminish the quality of life of those they afflict. And because these conditions affect more than 10 percent of the population, they constitute serious public health problems. For example, children with crossed eyes, "lazy eye", or myopia may have difficulty in school because of undiagnosed poor vision. Continued advancement of clinical investigation in this field rests upon an improved understanding of basic visual mechanisms. This program therefore supports both basic and clinical research aimed at the development of new methods for diagnosing and treating visual disorders.

Research is funded by grants and contracts, cooperative agreements, institutional training grants, and individual fellowships.

Rationale for the Budget Request

The 1991 budget request for the Strabismus, Amblyopia, and Visual Processing program is $42,939,000, an increase of $1,777,000 over the 1990 estimate. The 1991 request includes support for about the same number of projects as in 1990: 271 research project grants, 5 core grants, 20 grants in the other research category, and approximately 94 full-time-training positions.

Blepharospasm. Blepharospasm is an involuntary closure of the eyelids of both eyes, which is characterized by spasmodic contractions of the muscles surrounding the eyes. It typically occurs in middle-aged to elderly individuals and can progress to the point where activities such as reading, driving a car, or carrying out other normal visual functions are impossible. The cause of this condition, which may affect as many as 1,000 new people a year, is unknown. Treatment of blepharospasm with pharmacological agents or surgery has met with limited success. Recently, substances that are known to block the contractile properties of muscle have been used to weaken the contractions of the affected eye muscles, thereby improving the symptoms of patients with blepharospasm. The NEI has recently funded two new studies aimed at using this muscle blocking strategy. Drs. Linda K. McLoon and Jonathan Wirtschafter of the University of Minnesota Medical School will determine if doxorubicin, an antibiotic known to have a toxic effect on muscles, can be successfully used as a treatment for blepharospasm. In a related study, other investigators will determine if ricin, a cell toxin, will permanently reduce eyelid muscle function. Both these studies will be carried out initially in appropriate animal models and will lead to controlled clinical trials if the preliminary studies are successful.

Accommodation. The process by which the shape of the eye's lens changes to focus on objects at different distances is known as accommodation. The relationship between accommodation and the development of myopia has been a controversial topic for many years. Animal models of myopia are now beginning to shed some light on this issue. A team of investigators in New York and Boston trained monkeys to perform a complex letter discrimination task for 2-3 hours per day at a distance of only 10 cm. One eye was treated with atropine which temporarily made it impossible to target with that eye. The untreated eye of three of the four monkeys in this experiment became more myopic because its axial length grew longer. This suggests that axial growth is stimulated when the animal is required to accommodate for a substantial part of its daily behavior. There has been great interest in this clinically because of the possibility (as yet unproved) that intensive near work early in childhood could lead to myopia.

The relationship between accommodation and myopia is not clear in all animal models, however. Dr. Joshua Wallman at the City University of New York has pursued how abnormal visual inputs affect the development of proper refractor in chicks. If the eye is made myopic by rearing the chick with a

translucent occluder over the eye and then allowing normal visual input, the eye slows its further axial growth until it achieves emmetropia. If it is made (hyperopic) farsighted by dark-rearing to achieve corneal flattening, subsequent normal stimulation results in axial elongation, even though the eye is already longer than normal eyes of the same age. However, accommodation is not necessary for this effect; for this effect is still obtained even when a crucial part of the brainstem that controls accommodation (the Edinger-Westphal nucleus) is destroyed. A similar result was obtained, by Dr. Wallman in collaboration with an investigator at Cornell. Chicks were raised with either positive or negative lenses over their eyes, making them myopic or hyperopic, respectively. In this case, the eye should grow into an abnormal shape to achieve functional emmetropia with the lenses. The eyes did indeed grow in opposite ways to compensate for the imposed refractive error. This was also true if the Edinger-Westphal nucleus was destroyed.

Visual Perception. Dr. William T. Newsome of Stanford University and his colleagues have addressed a fundamental question in visual perception. They have done this by recording the activity of cells in the middle temporal (MT) area of the brain of a monkey while that animal is attempting to carry out a perceptual decision--discriminating an array of moving targets. They not only found nerve cells whose activity could be correlated with the stimulus perceived by the animal, they also found single nerve cells that responded to the moving stimulus even though the animal showed no behavioral response. For other cells in this part of the brain, they observed a trial-by-trial relationship between the intensity of the nerve cells' response and the perceptual judgment made by the monkey. These findings suggest that perceptual decisions in this task are related in a relatively direct manner to the movement information encoded by this class of nerve cells. The other significant finding from this study is that only a very few nerve cells in this particular area of the monkey brain are required to carry out this task. This implies that perceptual judgments could be based on the activity of a relatively small number of nerve cells in the monkey and in humans as well. Further research on the relationship between the activity of cells in parts of the brain responsive to visual stimuli and our perception of those stimuli, including mechanisms of visual attention, will continue to receive high priority in this program.

Workshop on Animal Research Protocols. Recent revisions to PHS policy and the NIH Guide for the Care and Use of Laboratory Animals and amendments to the U.S. Animal Welfare Act have heightened the awareness of neuroscientists and veterinarians that protocols using mammals in neuroscience experiments must be designed and performed in a humane manner that complies with these guidelines. One of the major challenges in this area lies in devising standards which Institutional Animal Care and Use Committees (IACUCs) can apply in complex neuroscience experiments. To meet this need, a workshop was held in June on the NIH campus entitled "Preparation and Maintenance of Higher Animals During Neuroscience Experiments." The goal was to bring together scientists and veterinarians to produce a document that will provide

supplemental information to IACUCs at universities to aid in their evaluation of research protocols involving neuroscience studies using higher animals. This workshop was sponsored by NIH and organized by the NEI.

National Eye Institute

Intramural Research

Authorization: Indefinite

Budget Authority:

1990 Appropriation		1991 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA
156	$23,615,000	161	$26,256,000	+5	+$2,641,000

Purpose and Method of Operation

The Intramural Laboratory and Clinical research program of the National Eye Institute has seven components: the Clinical Branch, the Laboratory of Sensorimotor Research, the Laboratory of Molecular and Developmental Biology, the Ophthalmic Genetics and Clinical Services Branch, the Laboratory of Immunology, the Laboratory of Retinal Cell and Molecular Biology, and the Laboratory of Mechanisms of Ocular Diseases. This budget activity also includes the Biometry and Epidemiology Program.

Rationale for the Budget Request

The 1991 budget request for intramural research is $26,256,000 an increase of $2,641,000 over the 1990 estimate. This level will provide funds for built-in increases in services provided centrally, personnel expenses, research supplies and services, and animal care facilities requirements.

The NEI intramural program has developed a multi-disciplinary research strategy to determine the causes of blinding and disabling vision disorders. This strategy integrates laboratory and clinical research and makes use of animal models to develop treatments for such human disorders as uveitis, diabetic retinopathy, retinitis pigmentosa, eye movement defects, resulting from neurologic deficits and maturity-onset cataract.

Intramural scientists have been able to prevent experimentally induced uveitis, a severe ocular inflammation that can result in blindness, by feeding laboratory animals the antigenic protein that induces this destructive immune response. They will soon begin the oral administration of this antigen to uveitis patients. The oral administration of the antigen induces T-cells of the immune system to suppress the uvetis. This autoimmune disease is sometimes difficult to control with immunosuppressive agents, and these agents

often have serious side effects. A new therapeutic approach such as this would be highly beneficial.

In related experiments, NEI investigators have used molecular biologic probes to isolate a unique protein from the surface of specific white blood cells that cause the uveitis in animals. They now plan experiments designed to prevent the expression of uveitis by vaccinating test animals with this protein. Comparable studies are under way with the immune cells of patients in preparation for attempts to control human uveitis in the same way.

The molecular biologic approach is also being used to neutralize the specific white blood cells that cause graft rejection. Using this technique investigators hope to treat patients in whom retinal cells have degenerated or been destroyed. By transplanting living retinal cells into the back of the eye without inducing rejection, they hope to restore vision that had been lost to disease.

Research on the organization of rhesus monkey brain cells into functional circuits that control eye movements has contributed nearly all that is known about similar functions in the brain of man. Advances in mapping the circuits that underlie the generation of rapid, or saccadic, eye movements have been used to develop exact measures and a better understanding of a disease of this system in man, progressive supranuclear palsy. Other experiments measure the loss of control of eye movements following very small lesions in the monkey brain . This model is being used to elucidate the factors affecting recovery of brain function which will be directly applicable to human patients recovering from stroke.

NEI scientists have developed a precise model of human diabetic retinopathy in galactose-fed dogs. These studies clearly demonstrate that retinal vessel changes occur that are similar to those seen in humans, including hemorrhages and the loss of pericytes, cells that are essential for the integrity of retinal capillaries. These changes occur because an enzyme called aldose reductase converts the high levels of sugar in the blood to sugar alcohols in the pericytes. Accumulation of sugar alcohols in the pericytes leads to cell death and the subsequent breakdown of the capillaries. Inhibitors of the enzyme are effective in preventing this destructive process if administered early enough in the course of the disease. These scientists have found that significant retinal pathology occurs prior to the appearance of retinal hemorrhage, and they are using the dog model to develop ways to detect earlier clinical retinal changes. Simultaneously, treatment studies with aldose reductase inhibitors are being conducted to determine the earliest point at which the disease can be arrested. Noninvasive methods for assessing aldose reductase activity in target tissues are being developed using nuclear magnetic resonance spectroscopy. This will permit rapid evaluation of the efficacy of new, more potent types of inhibitors now being developed. These studies may have direct application in the control of the clinical complications of diabetes, particularly retinopathy and neuropathy.

Investigators studying the causes of maturity-onset cataract have found that certain oxidation reactions produce permanent and cumulative changes in lens proteins. In particular, oxidation of the amino acid, histidine, a component of all proteins, results in a cross-linking of the proteins that causes a loss of lens transparency. NEI scientists are developing lens cell culture systems to test potential anti-cataract drugs that would block the oxidation reactions or counteract their effects.

NEI scientists continue their research on the structure and function of genes vital to the normal development and transparency of the lens. Malfunction or mutation of these genes may also lead to cataract, one of the serious eye disorders prevalent in the United States and throughout the world. These scientists have recently discovered that many of the major lens structural proteins, called crystallins, are found at lower levels outside the lens, where they have additional, nonstructural functions. Some serve as metabolic enzymes, while others have important, but as yet undetermined physiological functions. These discoveries suggest that the crystallins have a metabolic as well as a structural role, as previously believed. Investigators have identified regulatory elements on the crystallin that direct the production of the crystallins specifically in the lens. They have also found a protein that binds to this regulatory element and appears to be necessary for its lens-specific activity. The identification of DNA sequences that can direct the expression of a gene with lens specificity may one day permit genetic engineering in the visual system and brings us one step closer to gene therapy for certain eye diseases.

Investigators have been engaged in a study of a dog model that closely resembles the blinding human disorder, retinitis pigmentosa. This disease affects approximately 100,000 Americans, is characterized by the progressive loss of photoreceptors and ultimately leads to blindness. Although the human disease can take several decades to produce blindness, the dog model progresses to blindness in two to three years. Studies have centered on the metabolism of lipids or fats in the light-sensing photoreceptor cells of the retina. The light-gathering membranes of these cells normally have an unusually high level of the fatty acid docosahexaenoic acid, or DHA, which is derived solely from dietary fatty acid sources such as linolenic acid. The scientists found that the normal conversion of dietary fatty acid to DHA is very low, if at all, in the photoreceptors. They also found that the affected dogs, compared to healthy dogs, have low levels of DHA in their plasma, suggesting that some other organ, probably the liver, is deficient in converting dietary fatty acid to the DHA needed for healthy photoreceptor function. Animals raised on diets without essential fatty acids are known to suffer from severely impaired visual function. Thus, the dog model provides an opportunity to determine whether dietary supplementation with DHA can prevent or arrest the progression of this blinding disease. The results of these studies may be directly applicable to humans because low blood levels of

DHA have been found in certain groups of retinitis pigmentosa patients.

Biometry and Epidemiology Program

The primary mission of the Biometry and Epidemiology Program (BEP) is to plan, develop, and carry out human population studies concerned with the causation, prevention, and treatment of eye diseases and vision disorders. This includes studies of incidence and prevalence of disease in defined populations, prospective and retrospective studies of risk factors, natural history studies, clinical trials, genetic studies, and studies to evaluate diagnostic procedures. The BEP also carries out a program of education in biometric and epidemiologic principles and methods for the vision research community and provides biometric and epidemiologic assistance to the NEI scientific staff.

The program to evaluate new treatment strategies for diabetic retinopathy, a serious complication of that disease, continues to report significant findings. One study recently demonstrated that aspirin therapy does not lead to vascular complications in the eye. Laser treatment in the macular portion of the retina has been shown to increase the chance for good vision. The results of a study of the effectiveness of Sorbinil, a new drug developed by Pfizer, Inc., will be reported soon. The four year evaluation of vitrectomy, a surgical procedure, extends and supports the previous report of its effectiveness in saving vision of eyes that are threatened by significant pathology in the retina. These studies are playing an important role in guiding clinical care of the patient with diabetes.

Participating clinics for a new study of risk factors for progression of age-related macular degeneration, one of the leading causes of blindness in older Americans, will soon be selected. Over four thousand participants at different stages of this disease will be followed over a ten year period to determine the causes of vision loss.

National Eye Institute

Research Management and Support

Authorization: Indefinite

Budget Authority:

1990 Appropriation		1991 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA
68	$9,006,000	68	$9,686,000	--	+$680,000

Purpose and Method of Operation

This budget activity provides salaries and other expenses for the Institute's two major administrative components. The Office of the Director is the focal point for decision making regarding the overall scientific and administrative direction of Institute programs. This staff includes the Office of Planning and Reporting; the Office of Financial Management; the Office of Personnel Management; the Office of General Administration; and the Office of International Program Activities. The Extramural and Collaborative Program (ECP) is responsible for planning, directing, and managing the extramural research and training activities of the NEI and for coordinating collaborative research activities involving NEI staff and extramural investigators. The ECP includes four Scientific Program Branches (Retinal and Choroidal Diseases Branch; Anterior Segment Diseases Branch; Strabismus, Amblyopia, and Visual Processing Branch; and the recently established Collaborative Clinical Research Branch), a Review and Special Projects Office, a Research Resources and Training Office, and an Extramural Services Branch.

Rationale for the Budget Request

The 1991 budget request for Research Management and Support is $9,686,000, an increase of $680,000 from the 1990 estimate. The request includes support for built-in expenses including support for services provided centrally, personnel expenses, materials, supplies, and other basic operating needs. In addition, the category includes funding for the National Eye Health Education program.

Office of Science Policy and Legislation

The Office of Science Policy and Legislation is responsible for NEI program planning, analysis, and evaluation activities, including the development and maintenance of a computerized management information system; for legislative and other program coordination activities; and for public information and scientific reporting, including media relations, health education, and scientific reporting services in support of the NEI's research programs.

Policy Legislation Planning and Evaluation Section

During the past year the Section staff worked closely with the Vision Research Program Planning Subcommittee of the National Advisory Eye Council in preparing for and conducting its meetings, including a public policy planning forum. At this forum, representatives from a number of scientific and philanthropic organizations that support vision research met to discuss and make recommendations on NEI policy issues of particular concern or relevance to the vision research community.

In addition, the Section was responsible for conducting a joint meeting of the Subcommittee and the chairpersons of the various scientific panels that will be involved in the development of the next long-range vision research plan so that panel composition, functions, and a timetable for completion of the plan could be discussed.

One of the primary activities of the Section is to respond to a variety of requests for information and report NEI program developments and accomplishments to the NIH, PHS, DHHS, Congress, and non-governmental organizations and individuals. These reports include areas of currently special interest, such as AIDS, biotechnology, diabetes, the human genome, low vision, neurobiology, prevention, and toxicology.

Scientific Reporting Section

In addition to conducting its public information activities, this year the Scientific Reporting Section (SRS) began the planning, development, and management of a new national health promotion and education program. The National Eye Health Education Program (NEHEP) is a natural extension of the Institute's activities in vision research--a final step in the continuum where research results are disseminated to health professionals, patients, and the public.

To launch the new program, the SRS convened a NEHEP Program Planning Conference, March 2-3, 1989, in Baltimore. The conference was attended by more than 65 participants from 38 professional, voluntary, civic, government, and private organizations who attended plenary sessions, workshops, and

exhibits. The purposes of the planning conference were to (1) initiate a cooperative effort to plan, launch, and conduct the NEHEP, (2) define NEI's role as coordinator of NEHEP and the role of intermediary organizations in the program, and (3) gain interest in, support for, and commitment to the NEHEP. The conference was well received by the participants, and produced several recommendations for developing the program in the coming months.

To encourage referrals to NEI-supported clinical trials, the SRS produced an update of its booklet, Clinical Trials Supported by the National Eye Institute. The booklet describes 20 ongoing clinical trials including three new studies: Central Vein Occlusion Study, Herpetic Eye Disease Study, and the Advanced Glaucoma Intervention Study. A bibliography from current and past trails is also included.

More than 1,500 copies of the booklet were distributed to eye health practitioners at the annual meetings of the American Academy of Ophthalmology and the American Academy of Optometry. Listing the booklet's availability in professional journals has resulted in hundreds of additional requests from all parts of the world.

SRS staff provided guidance and advice for a number of projects in support of the public and professional information activities of the Institute. Among them were a publicity campaign to bring new investigators into vision research from scientific fields not normally represented by NEI grantees.

In order to define the information needs of the public and health professionals who write and call the NEI for eye health information and materials, the SRS has implemented a data management system to analyze the thousands of telephone and written public inquiries it receives each year. For the first time in the Institute's history, a clear profile of requests for information is available to help SRS plan new programs and materials and assess the public's interest in eye health topics. For the six month period January through June 1989, the SRS handled nearly 9,000 inquiries. Two-thirds of these inquiries were received by mail, and one third by telephone. Questions cover a wide range of topics, with the greatest number concerning general eye disease information, treatment of eye diseases, and the outcome of vision research, including clinical trials.

International Programs

For the past several years, the NEI has taken an active role in several broad-based international studies of blinding eye diseases that continue to have a severe worldwide public health impact. Such programs are implemented through bilateral agreements with the U.S. government, other types of country-to-country programs, and collaborative activities with such entities as the World Health Organization (WHO), regional associations such as the Pan-

American Health Organization (PAHO), foundations, and private and voluntary organizations.

A collaborative research program that includes projects to prevent blindness from cataract and vitamin A deficiency has been developed by NEI and various groups in India, including the Indian Council of Medical Research. One study for which NEI provided technical consultation revealed an impressive reduction in childhood mortality associated with improved vitamin A nutritional status.

The leading cause of blindness among preschool-aged children in Asia is vitamin A deficiency. For a study in Nepal, supported by the Agency for International Development through the HHS Office of International Health, NEI is providing technical oversight to determine the most effective design for affordable programs to prevent nutritional blindness.

Extramural and Collaborative Program

The Extramural and Collaborative Program (ECP) manages and directs the broad extramural and collaborative research and training activities of the Institute. ECP seeks to identify and address more effectively opportunities and needs in vision research, and to maintain and improve upon the productive relationships that have been established with the research community and with other interested individuals and organizations.

A new grant mechanism, the NEI Clinical Trial Planning Grant (R21), has been designed to support the initial development of a clinical trial research plan. This one-year grant will provide investigators with a mechanism for early peer review of the rationale and need for a proposed clinical trial, of the study's general design features, and of the likelihood of successful patient recruitment and followup. Up to $50,000 (direct costs) will be provided to support the development of a detailed Manual of Procedures and the pilot testing of study procedures. At the conclusion of this initial funding period, it is expected that the investigators would be in a much better position to prepare detailed, thoroughly documented, applications for the full-scale clinical trial.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Detail of Permanent Positions

	1989 Actual	1990 Appropriation	1991 Estimate
ES-5	1	1	1
ES-4	6	6	6
ES-3			
ES-1	1	1	1
Subtotal	8	8	8
GS/GM-15	12	14	14
GS/GM-14	17	19	19
GS/GM-13	16	19	19
GS-12	15	17	17
GS-11	9	15	15
GS-10	1	1	1
GS-09	15	25	25
GS-08	3	3	3
GS-07	17	28	28
GS-06	6	19	19
GS-05	5	14	14
GS-04	3	3	3
GS-03	2	2	2
GS-02	2	2	2
Subtotal	123	181	181
Grades established by act of July 1, 1944 (42 U.S.C. 207):			
Full grade	3	3	3
Subtotal	3	3	3
Ungraded	3	3	3
Total, permanent positions	137	195	195

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Advisory and Assistance Services

For FY 1991, the Advisory and Assistance Services budget will be $214,000, $13,000 less than the FY 1990 level. These funds will continue to support individual experts and consultants, studies, analyses, and other evaluative activities. Among these initiatives is support for technical evaluation panels. The process of technical evaluation is a requirement of the NIH Peer Review process in assessment of various proposals, both in station support and research contracts. Expert and consultant requirements are used to advise the Institute in the conduct of data monitoring committees, on clinical trials, and other similar ad hoc advisory activities. Under the studies, analyses, and other evaluative activities category, an operations research contract would be supported. The major focus of the operations research initiative is to develop cost effective approaches for translating low cost technologies developed by NEI grantees. Cataract will be a major focus of this effort. The personnel appointments category includes support for additional meetings of the National Advisory Eye Council (NAEC). The NAEC has determined that such meetings are necessary to update its vision research plan.

With regard to internal advisory and assistance controls, when NEI program officials meet to discuss contract concepts and requirements for the upcoming fiscal year, a procurement staff person is present to provide expert advice regarding the execution of the procurement. This includes the identification of clearances required to effect the action. At the time the procurement is described, the specialist can usually identify whether the initiative required is "consultant services." After the requirement is approved for funding, the Administrative Officer, Ordering Official, and Deputy Executive Officer meet to discuss the procurement in-depth. The purpose of this discussion is to determine whether the requirement falls under the advisory and assistance services (AAS) definition, appropriate sub-object classification, and allotment codes. The procurement is examined against the official AAS definition point-by-point. If the requirement falls under the AAS, a project description is developed and submitted to the Deputy Executive Officer for clearance. At this point, if it is determined that further examination is required, the NIH Division of Management Policy is contacted to provided more expert advice. Most requirements are clear cut and are decided in the Institute's initial discussions.

In the case of small purchases, a checklist is furnished to and completed by the official requesting the procurement (Form 2544). The authorizing official examines the request for applicability to AAS guidelines. If there are uncertainties, detailed discussions and examinations similar to those utilized for large procurements are conducted.

THURSDAY, MARCH 15, 1990.

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

WITNESSES

DR. DAVID P. RALL, DIRECTOR

DR. WILLIAM F. RAUB, ACTING DIRECTOR, NIH

CHARLES E. LEASURE, JR., ASSOCIATE DIRECTOR FOR MANAGEMENT, NIEHS

DR. JOHN McLACHLAN, DIRECTOR, DIVISION OF INTRAMURAL RESEARCH, NIEHS

ROBERT C. PATRICK, BUDGET OFFICER, NIEHS

DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DHHS

INTRODUCTION

Mr. NATCHER. We take up next the National Institute of Environmental Health Sciences. We have Dr. David Rall, the director. Doctor, tell us who you have at the table with you.

Dr. RALL. Thank you. On my far left our budget officer, Robert Patrick. On my immediate left our executive officer, Charles Leasure, and on my right Dr. John McLachlan, our new director of intramural research.

OPENING REMARKS

Mr. NATCHER. Thank you. Now, Doctor, we will be pleased to hear from you at this time.

Dr. RALL. Thank you, very much.

I am pleased to be able to report on what has happened at NIEHS in the last year and where we hope to be going in the next year.

One of the most significant things that we have initiated this year is a new program in academic awards for environmental and occupational physicians. One of the problems in this field has been the lack of environmental health research and environmental health teaching in the medical schools.

This new effort, I think, will begin a major program to introduce environmental and its sister discipline, occupational health, into medical schools.

Our job in the research community is to identify those factors in the human environment that can cause diseases, that can affect human health. We try to look at the available information and identify gaps and fill them. I want to talk about four programs which are old programs and a few which are new. I would request my formal statement be included in the record.

INDOOR RADON

First, indoor radon. This has been discussed widely and is viewed as a moderately severe threat. I don't know how many of you saw the article in the Washington Times last week which suggested that it may not be as serious a threat as has been projected. With the help of this committee we have a very large study going on, the relationship between radon in the home, cigarette smoking, and the outcome of cancer. This will involve almost 4500 people. I think it will give us a very good answer in 2 or 3 years as to what the real threat is from indoor radon.

AIR POLLUTANTS

There has been much discussion about the Clean Air Act. The Senate seems to have reached some compromise and the House is deeply involved in holding hearings. Our research on various air pollutants continues. The findings of our six and now our 24 city survey underpin some of the conclusions of the needs in the Clean Air Act as enunciated by the Senate, the need for better determination of particulate in the atmosphere, a better understanding of the fact that it is the acidity in the air pollution that may cause some of the most serious effects on the lung.

OZONE

In terms of ozone, the irritating cloud that comes on the warm summer days typically in Los Angeles but also on the East Coast, our grantees have done some marvelous studies on school children on the East Coast on days when there was high ozone concentration. They have found that at the current standard, which is viewed as the maximum allowable concentration, exercising school children suffer a decrease in pulmonary function at those levels of ozone.

Now if children exercise in a chamber where they are exposed to clean air plus that amount of ozone, they seem to have no such effect. So it is clearly the ozone at the standards as well as the other air pollutants and particulates and the sulfuric oxide. This poses a serious problem because large segments of the East and West Coast exceed the ozone standard in the summer.

The flap about alar and apple contamination in the last year has raised the problem to a higher level of consciousness that most of our common pesticides have not been tested in laboratory and animal studies. We commissioned the National Academy of Sciences to do a study some years ago. That study suggested that perhaps as few as 15 percent of the pesticides had been adequately studied.

PESTICIDES

The House Agriculture Subcommittee performed a study looking at all the data bases in the Environmental Protection Agency and came to the same conclusion that between 80 and 90 percent of the pesticides in use today do not have adequate carcinogenic studies.

LEAD

Our research with lead continues. We are looking at the relationship, thanks to some help from this committee, of the movement of lead between the mother and fetus. In other words when a woman is pregnant does the lead she ingests go directly to the fetus or is it stored in the mother's bones? This has many practical implications.

Dr. Needleman in follow up to his Harvard studies looked at children he first looked at seven or eight years ago who had low to moderate blood lead levels, not high by any standard of the imagination. He found that among these children he looked at again, they had six to seven times a greater drop out rate in high school than normal children and six to seven times greater incidence of learning disabilities. In other words, low to moderate blood lead seven or eight years ago yields lasting serious effects.

CHRONIC RENAL DISEASE

I mentioned briefly our study on the cause of chronic renal disease and the need for dialysis treatment which cost the American taxpayers approximately $3,400,000,000 a year. We have been setting up and analyzing a large case control retrospective study using the very elegant hospitals in the University of North Carolina system. We are looking ultimately at environmental and occupational factors but first we needed to identify or look at some of the suspected causes including over the counter analgesics, diet, drink, and so forth.

The first compounds we looked at were over the counter analgesics, Tylenol® and others, the proper name is acetaminophen. We found the daily use of acetaminophen increases the risk of chronic renal disease three-fold. That is you have a three-fold higher chance of ending up in renal dialysis if you take acetaminophen daily for at least a year.

It should be pointed out that package inserts in that drug say do not take it for more than a short period of time, 10 to 14 days, before you see a doctor. Yet anecdotal studies tell us many people will take acetaminophen on a daily basis. We have preliminary evidence that other non-steroidal compounds, particularly ibuprofen, a powerful analgesic, causes a ten-fold increase in chronic renal disease in elderly males.

These two factors are totally preventable and could significantly reduce chronic renal disease. Aspirin does not have this effect. Although aspirin does have some problems with bleeding in the stomach, if you take plenty of water with the aspirin that should not be a problem and daily use of aspirin does not pose a threat.

By next year, I will be able to bring you more information on food, drinking, life style, et cetera. But simply better use of over the counter anti-pain killer, and analgesics would cut the incidence of long-term renal disease significantly.

CHEMICAL TESTING PROGRAM

In terms of our chemical testing program we found some interesting positives. Tetranitromethane, which is an intermediary on the way to making explosives and in which factory workers are in-

volved, is very powerful. We are working with NIOSH and OSHA to identify those people who might be at risk. Glycidol, a chemical under very wide use is very serious as a carcinogen.

Three others have no chronic toxicity, amphetamine, mace, the riot control agent, and vinyl toluene, a widely used intermediate in chemistry. This is just a sample of the results that are on-going.

PREVENTION

We are looking for preventable causes of disease which, as we all know in this sense, is the most efficient way of preventing renal ill health and decreasing cost of disease. As the cost of health regulation becomes increasingly high, apparent in the debate in the Clean Air Act, this is one of the paramount factors. It seems to me it is clear that the better information we have on the human health impact of the various pollutants controlled or not controlled by the Clean Air Act, the better legislation can be written, legislation that is most efficient in terms of minimal exposure, maximum health benefit.

Mr. Chairman, our budget request this year is $235,792,000. I would be pleased to answer any questions.

[The information follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Institute of Environmental Health Sciences

The National Institute of Environmental Health Sciences (NIEHS) leads the nation and the world in basic research into the human health effects of environmental exposures.

We take so much in the environment for granted; we assume the necessities of life will always be there for us. As we move into the final decade of the 20th Century and toward a new millenium, we know of some things that will persist. We must have air to breathe. In general, we would die in less than 10 minutes without air. We would die after about three days without water to drink.

Beyond these most essential requirements of human life, we need food, shelter, and places to work to earn the food and shelter. Each of these is a part of the human environment. Each affects human health, and may affect health in a number of ways. Our quest for the necessities of life has altered our environment in ways that have imperiled some of these necessities themselves.

Much of what we understand today about the human health impacts of human activities in the environment, the interaction of environmental agents and human health, has been developed through the basic research programs of the National Institute of Environmental Health Sciences. Many committee members will recall that asbestos was one of the first research topics I brought to you, and it came up again and again. Asbestos is still with us, but we have a much better understanding today of its health effects, because of NIEHS research.

Our programs address the information gaps of both old and new environmental public health challenges. Research we support continues to expand our knowledge about lead, one of the oldest human-spread environmental contaminants. Our recent conference on the potential impacts of global warming on human health was the first to probe that emerging set of questions.

We are only now beginning to understand the human health dimensions of the way we use and dispose of our resources-- in the air, the water, or the land.

NIEHS-supported scientists studying the effects of air pollutants on human health have identified both key air pollutants and lung damage that exposure to pollutants, alone and in combination, can cause. Ground-level ozone has been confirmed as a factor in lung damage in studies of healthy youngsters. NIEHS is also pursuing efforts to define the effects of depleted stratospheric ozone on human immune systems. That association stems from more ultraviolet light reaching the earth when the ozone shield is depleted. A portion of our budget request will support continued efforts toward defining and understanding the human health effects of air pollution, including the large study of indoor radon exposure we told you of a year ago.

The human ability to produce new chemicals, like those that have been used to grow larger crops of food and fiber, has outstripped our ability to anticipate and avoid unnecessary exposure to the chemicals both directly and through various paths. A portion of our budget request will go to projects studying the human health effects of pesticides and to developing safer approaches, from the human perspective, to controlling pests.

The recent report on the long-term effects of lead, an early and continuing topic of research supported by NIEHS, indicates that the social cost of human exposure to lead may grow with time as those damaged early in life continue to falter and may be labeled slow. The damage from lead is not confined only to the well-characterized, early effects of lowered mental function and, in the heavily exposed, organic damage and seizures. New NIEHS initiatives include a study of the way lead is transferred from mother to fetus, the way the body stores lead over time, better methods for measuring lead levels in humans, and development of improved therapies for those with high lead levels.

When we first discussed the need to identify potential human health effects of global warming, it was not obvious how sparse the information base was. Following the NIEHS conference on global warming and human health, that lack is much clearer. So are some considerations for public health, from possible new ranges for insects that carry disease to the effects of altered nutrition from altered food crop availability, heat stress, and potential effects of new products and processes used to try to alter the pace of change. These were among the topics at our conference, the first to address that subject specifically.

Meanwhile, our scientists are studying today's challenges in health effects and diseases linked to environmental exposures, seeking things we might do now to ease the burden of such disease.

I want to report on the first results of an NIEHS epidemiological study on the environmental factors that may contribute to end stage renal disease.

Kidney disease is an expensive national public health challenge. Recent data from the national renal disease information base indicates dialysis cost the nation $3.5 billion in 1988. The cost in human suffering and economic productivity for those with end stage renal disease has not been quantified.

The incidence of kidney disease is higher in the southeast than in other regions of the country and there have been a number of theories about why this is so. Our epidemiologists designed a study to look at what is really going on. This long-term study has focused on identifying preventable causes of kidney disease.

Our investigators sorted through the well-known associations with hypertension, diabetes and other systemic diseases. Among the environmental suspects are solvents and other chemicals; lead, cadmium, and other metals; and a variety of drugs including nonsteroidal anti-inflammatory drugs, other analgesics, antibiotics, high blood pressure medications and diuretics. Environmental influences as contributors to renal disease for people who have high blood pressure or diabetes are also being considered.

The study found that daily users of acetaminophen analgesics had three times the risk of developing renal disease as those without this pattern of use, and the data supported a dose response. Daily use of phenacetin, a related compound removed from the over-the-counter market some time ago, was linked to a five-fold increase in risk for kidney disease. Daily users of other non-aspirin, nonsteroidal anti-inflammatory drugs were twice as likely as non-users to develop chronic renal disease, but the risk was concentrated among older men, who had 10 times the risk of non-users.

Still being analyzed are the possible influences of caffeine, alcohol, cola beverages, and related lifestyle factors.

The molecular basis of cancer evidently involves two opposing forces: oncogenes which lead to cancer and suppressor genes which inhibit cancer. Both sides of this equation are under intensive investigation at NIEHS. A single human chromosome, chromosome number 1, seems to determine whether or not tumor cells continue unlimited growth in culture or grow old and die. These studies may provide a molecular basis for tumor suppression. A novel oncogene is activated in human mesoltheliomas, a highly malignant tumor associated with exposure to asbestos. Future efforts could lead to the development of a diagnostic marker for either preclinical disease or exposure to other toxic fibers, and, possibly, to potential treatments.

We continue to share information and foster communication among scientists, policymakers and the public about where the need for more and better information is greatest. Two significant examples of this effort may be seen in meetings during 1989 on the Alaskan oil spill and on methylmercury.

The oil spill conference brought up, for the first time in such a forum, questions about potential human health effects of exposure to the crude oil in Prince William Sound. In addition to effects on wildlife and aquatic life that may have implications for people, conference participants identified exposures with potential health consequences for cleanup workers and those who live near the oiled shorelines. Short- and long-term physical, medical, and psychological impacts of the spill and its aftermath were among the considerations.

Mercury, in its toxic methylmercury form, is emerging as a more ubiquitous environmental agent than had been realized. In the NIEHS conference, scientists discussed emerging evidence of adverse effects on the unborn at very low levels of maternal exposure to methylmercury. Recent studies have examined mercury fallout into lakes after long-distance air transport, the ensuing change in chemical form--methylation-- and subsequent mercury in food fish that may find their way to the table. Scientists noted that lakes with acid water seem to have more methylmercury in the water and in the fish. Another agency's study, reported in January, noted the increasing numbers of acidified U.S. lakes, especially in the East and the upper Midwest.

Brazil offers an example of the variety of sources for mercury emissions to the global winds. Brazil's massive chloralkali paper processing plants and an entrepreneurial gold mining industry where blowtorches are used to separate gold from dirt and mercury account for large quantities of mercury that eventually contaminate lakes and rivers and the fish in them.

I am pleased to report that we are beginning an Environmental and Occupational Medicine Academic Awards program with the dual purposes of improving the quality of environmental and occupational medicine curricula and of fostering research and careers in environmental and occupational medicine. This effort addresses concerns outlined in an Institute of Medicine report. For this award, the term environmental and occupational medicine is used to define the medical area that has special concern for the development and application of knowledge for the diagnosis and treatment of adverse human health effects from environmental and occupational exposures to environmental agents.

And finally, the National Toxicology Program's testing program produced 27 printed technical reports on chemicals in fiscal 1989, and had 21 technical reports and eight toxicity studies peer reviewed. From that program, which is considered the world standard for such testing, NTP issued the final report on tetranitromethane, a rocket propellant and explosive that rapidly produced many lung tumors in test animals. The NTP had alerted the Department of Defense, the agency responsible for plants where the chemical is used, NIOSH and OSHA when the early results appeared.

Other chemicals positive for cancer in NTP tests included glycidol, a stabilizer in vinyl polymers and an additive for oils and hydraulic fluids; nalidixic acid, a pharmaceutical ingredient which caused cancers in rats but not in mice; 4-vinyl-1-cyclohexane diepoxide, used in epoxy resins, which caused cancer in all exposures-- male and female rats, male and female mice; and hydroquinone, a metabolite of benzene and a chemical used in photography. On the other hand, chemicals that did not cause cancer in NTP tests included amphetamine, which is a pharmaceutical, the riot control agent mace, and vinyl toluene, an important industrial chemical.

Mr. Chairman, the budget request for the National Institute of Environmental Health Sciences is $235,792,000. I would be pleased to answer your questions.

RALL, DR. DAVID P.
Director, National Institute of Environmental of Health Sciences
and Director, National Toxicology Program

August 3, 1926. Aurora, Illinois

Education: B.S. North Central College, 1946; M.S. (Pharmacology), Northwestern University, 1948; M.D., Northwestern University School of Medicine, 1951; Ph.D. (Pharmacology), Northwestern University, 1951.

Professional History: 1952-53, Intern, Bellevue Hospital. 1953-58, Scientist, Laboratory of Chemical Pharmacology, National Cancer Institute. 1958-63, Head, Clinical Pharmacology and Experimental Therapeutics Service, General Medicine Branch, National Cancer Institute. 1963-69, Chief, Laboratory of Chemical Pharmacology, National Cancer Institute. 1966-71, Associate Scientific Director for Experimental Therapeutics, National Cancer Institute. 1971-present, Assistant Surgeon General, USPHS.

Professional Organizations: American Association for the Advancement of Science, American Association for Cancer Research, American Public Health Association, American Society for Clinical Investigation, American Society for Pharmacology and Experimental Therapeutics, Society for Occupational and Environmental Health, Society for Risk Analysis, Society of Toxicology.

Honors, Awards: Editorial Board, Proceedings of the Society for Experimental Biology and Medicine, 1962-65. Member, National Institutes of Health Chemotherapy Study Section, 1965-67. PHS Meritorious Service Medal 1966. Chairman, National Institute of General Medical Science Pharmacology Toxicology Review Committee, 1967-69. Editorial Board, Pharmacological Reviews, 1969-72. Chairman, DHEW Departmental Committee on Drug Research and Regulations, 1970. Associate Editor, Cancer Research, 1970-74. Chairman, OST-CEQ Ad Hoc Committee on Environmental Health Research, 1971-72. Adjunct Professor, University of North Carolina, Chapel Hill, 1972-present. US Coordinator, Environmental Health Program, US-USSR Health Exchange Agreement, 1972-present. Chairman, DHHS Committee to Coordinate Environmental and Related Programs, 1973-1985. Editorial Board, Archives of Environmental Health, 1973-76. Associate Editor, Journal of Toxicology and Environmental Health, 1974-78. DHEW Distinguished Service Medal, 1975. Member, DHEW Secretary's Review Panel on New Drug Regulation, 1975-76. Member, NAS Safe Drinking Water Committee, 1975-1977. Chairman, Committee on Health and Environmental Effects of Increased Coal Utilization, 1977-78. Member, Institute of Medicine, 1979-present. Editorial Board, American Journal of Industrial Medicine, 1980-present. Member, WHO Programme Advisory Committee, 1980-present; Chairman, 1980-81. Editorial Board, Risk Analysis, 1981-present. Editorial Board, Regulatory Toxicology and Pharmacology, 1981-present. Arnold J. Lehman Award, Society of Toxicology, 1983. Member, US Delegation to the US-Japan Cooperative Medical Science Program Committee, 1984-present. Member, Committee on Council Affairs, American Association for the Advancement of Science, 1986-88. World Health Organization "Health for All 2000" medal, 1988. Ramazzini Award, 1989.

Mr. NATCHER. Dr. Rall, what can you tell us about the findings from your recent conference about the problem of global warming?

Dr. RALL. We held that conference on global warming the last few days of July in Seattle, Washington, to be as close as we could to the oil spill in Prince William Sound. The oil spill occurred just 10 days short of a year ago.

Let me first make one broad comment: our meeting was, as I said, in the last few days of July. There were no good data presented in terms of the contamination by the oil of the seafood in the immediate area of Prince William Sound or in the adjoining areas which are used extensively for commercial fishing.

It is the first scientific meeting we have ever held like that when there simply were no data involved. To me that is very worrisome.

Mr. NATCHER. Doctor, you are ahead of us; we asked about global warming as far as the conference is concerned?

Dr. RALL. I am sorry, I thought you asked me about the oil spill.

Mr. NATCHER. On global warming, we read articles in the paper about 1 percent warmer now, et cetera. What can you tell us about these issues?

Dr. RALL. Yes, sir. We were very concerned that no one seemed to be concerned about the health effects of global warming. They were concerned about agricultural productivity, the eventual rise in the sea level. We felt there could well be serious direct and indirect effects on human health. We assembled a group of atmospheric chemists as well as very good scientists to try to look at this. The direct effects—I don't know whether global warming is going to happen or not.

This is obviously highly debated and I am afraid it is becoming polarized. All you had to do is enjoy yesterday afternoon in Washington, 90 degrees in March, and you must wonder about the effect of global warming. Obviously, it will be hotter, the increase in nonmelanoma skin cancer will happen almost assuredly, and in melanoma skin cancers since there is an uncertain but real relationship with that.

Cataracts probably will increase but probably not as much as people might have worried about. There are disturbing signs that the immune system is depressed in laboratory animals. This has not been demonstrated in humans but it is something that should be looked at. There is another effect that is not yet well recognized and that is increased photoactivation in humans of toxic chemicals. Many chemicals we ingest such as the sulfonamides, et cetera, are altered by the ultraviolet rays in the skin and activated into more toxic compounds. As we get shorter wave lengths we can expect more unexpected toxicity from chemicals.

In addition the greenhouse gases are also many of the irritant gases which will cause more pulmonary damage and toxicity. Those are the direct effects. We are reasonably certain of them. Whether they will be serious or mild, we don't know.

There are indirect effects that can be very much more serious such as redistribution of the food supply. There probably will be no net decrease but it will occur in different areas. This could lead to mass migrations of a very large magnitude which could be serious.

Increased range of a variety of noxious pests. If it gets warmer in the Washington area, it is possible that the anopheles mosquitoes which carry malaria can live here.

A pest which carries yellow fever and some of the encephalitis can also become more common. Malaria: we have treatment, prevention and cure for many strains but others are becoming resistant to what we have. Even in the current areas, the control of malaria is not very good.

The three viral diseases, dengue, yellow fever and encephalitis, there is a vaccine for yellow fever, a very painful and not very effective one. But we cannot treat the others, dengue and yellow fever—once it is established—and the encephalitis. It is a serious problem. It is these problems we worry about and we expect there should be an added research effort, some at our institute and some for instance at the National Institute of Allergy and Infectious Diseases. This is sort of a prevention treatment in case global warming develops fully.

BUDGET SHORTFALL

Mr. NATCHER. Doctor, as you know, the President's budget proposes only a 2.8 percent increase for your institute which is less than half of what we are told is the rate of inflation in biomedical sciences.

How will you deal with this shortfall briefly, doctor. How will you handle it?

Dr. RALL. We are simply moving less rapidly than we would like to move. We will be able to keep our programs going, although not quite as well as we would like, but we will maintain some momentum in all the programs.

REIMBURSABLE FUNDS

Mr. NATCHER. Now in previous years you also described the part of your work which is financed from other sources. The budget materials that we have indicate that this will increase from $27,700,000 in 1989 to $41,500,000 in 1990. This, as you know, is $14,000,000 more than you expected when the 1990 budget was submitted.

Will that have a direct off-setting effect on requirements under the appropriation which we are reviewing today?

Dr. RALL. The $14,000,000 plus will fund two separate programs. The first program is the worker health and safety training program which is not one of our typical programs. We give grants to non-profit organizations to directly train workers involved in toxic chemical waste. That will go from a little under $10,000,000 to a little under $20,000,000. This is a very good program, we are very pleased with it. We have already trained 30,000 workers in this field. It will not offset the other efforts.

The basic research and development program in university centers will increase by about $4,800,000. Those centers are interdisciplinary and deal not only with human health effects but ecology, hydrology, et cetera. They will be very useful but they will not directly offset the sort of human health studies that we need.

RESEARCH TRAINING

Mr. NATCHER. Approximately $10,500,000 of your budget is set aside for training. Are you able to attract the types and quality of trainees that you are looking for?

Dr. RALL. I think so. I talked to the directors of our training programs. Mostly, they say they are getting very good people. But there are some areas where it seems that the MBA may be more popular than the Ph.D. Perhaps some of the things that happened in Wall Street in the last 2 or 3 months may redivert some of these people into biological research.

Mr. NATCHER. Thank you.

Mr. Conte, I yield to you.

BERKSHIRE ENVIRONMENTAL HEALTH INSTITUTE

Mr. CONTE. Thank you, Mr. Chairman.

Dr. Rall, I join Chairman Natcher in welcoming you before us today. Your institute has been the pioneer in environmental health. You have been on the cutting edge on acid rain, global warming, material hazards and many other health issues of national and international importance. We on this committee look forward to working with you to improve the health of both our people and our environment.

Berkshire Environmental Health Institute, last year, funds were provided to continue support of ongoing efforts to assess and interpret data related to the biological and clinical effects of chemical and physical agents in our environment. For example, the Berkshire Environmental Health Institute, with Dr. Bloom leading the way, is going full speed ahead on issues like the genetic cause of cancer, oxidation damage, and risks of toxins on reproductive health. They have done a terrific job.

Is this project included in this year's budget request?

Dr. RALL. Yes, they have done a very good job. Their work is in the budget.

ALASKAN OIL SPILL

Mr. CONTE. Thank you.

As you mentioned in your written statement your institute held a major conference on the health effects of the Alaskan oil spill. I went and looked at it. Crude oil contains a whole blend of toxic chemicals. Lots of high octane. Can you share with us what is known about the health risks of these spills on clean-up workers and local residents?

Dr. RALL. As I inadvertently began to discuss, we are very discouraged that we cannot get the information out of this particular oil spill. Now it is known that the fresh oil is quite toxic. It has so-called volatile components in it such as benzene which are known to be carcinogenic and can cause destruction of the blood forming system, et cetera. It has the benzopyrine type complicated carcinogens and other toxic agents.

As the oil weathers it tends to get somewhat less toxic. But clearly for some years it is very detrimental to the wildlife, to the sea life, et cetera.

Mr. CONTE. How about human health?

Dr. RALL. In terms of human health it is irritating. It can cause skin lesions and can also lead to cancer if there is enough exposure. The Exxon workers and the clean-up workers they hired appear to be reasonably well protected with their clothing which is the only way you can do this. Working conditions were very difficult. The workers lived on dormitory boats. They came in and out of the boats. I think the only fatality was drowning or a person crushed by an elevator, one or the other.

We were able to work with NIOSH and the University of Washington to get a health evaluation of those workers. Alaska has a good occupational health service which will follow them. The subsistence of the three villages will be wiped out for at least one year and probably longer. This can have very serious effects on those Alaskan natives. The commercial fishing seems to be spared but there is not a program of sampling fish and other seafood. We will have a conference late this summer and see what the results are 1 year later.

Mr. CONTE. I was up there testing the waters. Even though the water looked clear above as I moved around and hit the bottom it would raise white rings of oil on the surface. So that oil will be embedded in there for a long period of time.

Dr. RALL. It can get embedded by sand in the coastal areas and it will reappear unexpectedly.

SHORTAGE OF SPACE

Mr. CONTE. Doctor, I hear you are getting short on space at your headquarters down there in North Carolina. Is that correct?

Dr. RALL. A third of the people are in the original buildings built in the mid to late 1960's which were built not as permanent but as temporary rental space. They have a life expectancy of 20 years. Quite clearly that was a good estimate of their life expectancy. My office is now on the new campus with a wonderful facility that this committee helped provide for us.

But in the old facility, I moved into my new office one day in Building One, it was very cold. We could not figure it out. We finally moved the curtains back by the window. The building had just sunk away from the window so there was a 2-inch gap and cold air was coming in. That is typical. They were fine structures put up in a hurry. The institute was able to move in and get going. They are increasingly expensive to maintain and increasingly expensive to provide utilities for. The air handling equipment is inadequate for safe handling of toxic chemicals. There is a fair amount of recirculation of the air in the laboratories and this is really very bad.

We have plans, thanks to this committee's actions, to add a modest expansion to each end of our building and completely get out of this temporary rented facility. Those would cost in the order of $55,000,000. We would save in the order of $4,000,000 a year, direct, precise savings that we can quantify, by building and moving into those facilities and consolidating our operations under one roof.

This would make us much more efficient.

COLLEGE CHEMISTRY LABS

Mr. CONTE. We will do all we can to help. You have been looking at many toxic substances in a variety of occupational and residential settings. One area I think you have to look at is the college chemistry labs. Here is a situation where you have young inexperienced students working in an environment that contains literally hundreds of different types of chemicals, benzene, toluene, sulfuric acid and many others.

Meanwhile we are all upset about having one part per million in Perrier. Have you considered looking in the school chemistry laboratories as a potential health risk?

Dr. RALL. We have worked with the group some years in this. Things look a little better. We were aware of some of the more toxic chemicals. I think it would be a good idea to look again. We know more about the chemicals and we will in the next year work with the education association and survey this and see if it is a problem.

Mr. CONTE. Are there any guidelines in the construction and operation of these labs?

Dr. RALL. There are guidelines for the construction and operation of any laboratory that uses toxic chemicals. These labs should follow those guidelines.

SIX CITY SURVEY

Mr. CONTE. There were allegations that a Harvard professor hid mistakes involving the six cities air quality study a long running and important project. Are there any serious and uncorrected errors that might have an impact on developing the national air quality standards? What is the status of that investigation and is there any fall out of this investigation that would have impact on the air quality standards?

Dr. RALL. We were very concerned about these allegations by one ex-employee about serious errors in the data base. I have personally talked to all of the Harvard people involved and I am convinced that there is no problem. The person who made the allegation has since dropped it. But it is my understanding, and I am very pleased, that NIH will continue to investigate to insure that there are no problems with that very critical data base.

Mr. CONTE. Thank you, Dr. Rall.

Thank you, Mr. Chairman.

Mr. NATCHER. Mr. Obey, I yield.

CABINET LEVEL FOR ENVIRONMENTAL PROTECTION AGENCY

Mr. OBEY. Thank you, Mr. Chairman.

Dr. Rall, good to see you. I apologize. I have to make these questions short because I have to get back to another hearing.

Let me first ask you, we hear a lot of talk about creating a new cabinet at the Environmental Protection Agency. I think that we often give people chairs at tables when we don't give them resources. It is sort of a consolation prize. Absent any new funding to help EPA carry out its mission, is there going to be any dramatic, noticeable change designating an EPA cabinet official?

Dr. RALL. You said the key words, absent any significant funding increase. I don't think you will make much difference. I think there is a psychological boost to the concept that the environment has finally reached a cabinet level of the United States rather than being relegated to simply an independent agency.

Perhaps it would be more tangible evidence that the Federal Government understands that environmental problems are very real, indeed.

NORTH CAMPUS FACILITY

Mr. OBEY. I have no objection to giving people an extra badge or a bigger badge. I think it might be helpful if you gave them resources to go along with it.

Let me ask you, the design for the North Campus, how long has that been ready?

Dr. RALL. It was really ready late last year.

Mr. OBEY. What is the status of your campus?

Dr. RALL. It is in pretty bad shape. Twenty buildings with 20-year life span designed and constructed between 1965 and 1969. They are showing their age. Systems break down, air conditioning systems don't work. They need to be replaced. There is inadequate electricity. They are very expensive to maintain.

Mr. OBEY. What is the minimum you would need to get that construction project started?

Dr. RALL. $15 million would let us get started.

ASBESTOS

Mr. OBEY. I have seen two articles that appeared in the New England Journal of Medicine regarding research done on asbestos.

As you know, I have more than a minor interest in that subject. Both articles conclude the available data does not support the concept that low levels of asbestos is a danger in buildings and school.

Are you familiar with those articles?

Dr. RALL. Yes.

Mr. OBEY. You do agree with their findings?

Dr. RALL. No. I am somewhat distressed by them. There is no original research in those articles. They are simply reviews. All the articles they cite are perfectly reasonable articles, but they only tell one side of the story. There are really two issues that they bring up.

One is that chrysotile, which is the common asbestos in the ceilings of schools and other buildings, is much less toxic and carcinogenic than other forms of asbestos.

The evidence for that, the evidence for its relative lack of carcinogenicity is presented in great detail in these articles; equally persuasive evidence that chrysotile is a serious health hazard is not presented. Even in very low doses, chrysotile is carcinogenic, can cause mesothelioma, and we should treat chrysotile as just as dangerous as any other form of asbestos.

The other issue about school room ceilings requires the application of common sense which so often seems to be missing. A perfectly solid asbestos cement ceiling that is in no danger of deteriorating is no hazard and should be left alone. A highly disintegrated

ceiling, friable asbestos, clouds of dust, that is obviously an immediate hazard.

It seems very clear to me that the latter you attack, the other you leave alone. There are, of course, all these grey areas in between. I think simply good sense would say that you try to be sure that the ceiling is intact. Then there will not be any problem.

This article says the average fiber count is very low, indeed. Certainly, if you sample rooms with an intact ceiling, the more you sample, the lower the average fiber count would be. But, that does not take into account the children, the teacher, the janitor who is involved in a room with a high fiber count.

I think you need judgment in trying to decide which ceilings to clean up.

NONASBESTOS FORM FIBER MATERIAL

Mr. OBEY. If you could just—let me ask you quickly some three remaining questions.

It is my understanding in the Federal Register OSHA is proposing not to regulate the nonasbestos form fiber materials, in your opinion, do those minerals differ greatly from asbestos? How many workers, in your best professional judgment, could we expect to see die as a result of exposure to nonasbestos form fibrous materials?

Dr. RALL. Nonfibrous materials seem to be either noncarcinogenic or much less carcinogenic. I have not read those regulations. I am not sure what they said. I would like to answer that for the record. I will give a good, complete answer.

[The information follows:]

NON-ABSESTIFORM FIBERS—OSHA NOTICE OF PROPOSED RULEMAKING

We have reviewed this proposal and have discussed it with NIOSH. They will be responding to this and we have made a few suggestions relative to their response.

There are two major problems with this proposal. First, is the definition of asbestos. Commercially, this is done on a macroscopic level; however, concern for biological response is at the microscopic level. At the microscopic level, it is not possible to distinguish a fiber which grew as a fiber in nature from a cleavage fragment produced by grinding and processing more masive, non-fibrous amphibole minerals. Furthermore, most mineral deposits wil contain true fibers as well as cleavage fragments. For example, New York talc operations contain a mixture of amphibole minerals including fibrous and non-fibrous tremolite, anthophyllite and fibrous talc. From OSHA's proposal, it is not clear how this would be regulated.

OSHA reviewed the animal and epidemiological data. The experimental animal data supports the position that particle morpholo,y is the most important factor relative to biological activity. Thus, it is somewhat irrelevant whether a particle of critical dimensions grew in nature of resulted from mechanical action and cleavage.

The epidemiological data do not provide sufficient evidence to negate the experimental animal data. Few cohorts have been studied where exposures were largely to non-asbestos cleavage fragments and the environmental data are sufficient to determine the levels of exposure to fibers of critical dimensions. New York talc studies by NIOSH clearly demonstrated excess lung cancer and non-malignant respiratory disease mortality at mean exposure levels of approximately 5 fibers per cubic centimeter. Studies of Homestake goldminers and taconite workers have shown less dramatic lung cancer excesses; however, exposures to fibers of critical dimensions in both of these populations is consistent with that predicted from dose-response data derived from asbestos exposed cohorts on a fiber-per-fiber basis.

The potential impact of OSHA's decision not to regulate non-asbestiform termolite, anthophyllite and actinoiite is difficult to estimate. Mining operations, except for crushed stone, are regulated by MSHA and are thus not covered by OSHA. However, OSHA's regulation would affect a large number of downstream users of mate-

rials such as talc, vermiculite, certain clay minerals, industrial sands, and so forth. The number of workers potentially exposed in these industries is not known.

TOXICITY TESTING NEEDS

Mr. OBEY. Could you provide for the record how many compounds are there that need to be researched to determine their toxicity in human beings? How many is NIEHS able to study each year? With this year's budget authority, how many will you be able to study? Could you submit funding levels of the chemical tested program over the past 10 years?

I have two other questions I would like to submit for the record.

CHEMICAL TOXICITY

A study by the National Academy of Sciences/National Research Council of the toxicity testing needs for 65,727 substances in our environment to which there is known or anticipated human exposure revealed that adequate studies for health hazard assessment were available for only 5 percent of food additives, 10 percent of pesticides, 2 percent of cosmetics, 18 percent of drugs, and zero percent of 48,523 chemicals in commerce.

The resources to the Institute to address this problem have changed little over the last decade. Annually we are able to start 10 chemicals for carcinogenicity, 15 chemicals for toxicological characterization, 150 chemicals for mutagenicity, 25 chemicals for developmental and reproductive toxicology, and 10 chemicals for immunotoxicology. The 1991 budget will allow the same level of testing as the past few years.

FUNDING FOR NIEHS/NTP CHEMICAL TESTING—(EXCLUDES METHODS DEVELOPMENT AND VALIDATION)

(Dollars in millions)

Year:	*Amount*
1982	46
1983	46
1984	49
1985	48
1986	51
1987	53
1988	52
1989	53
1990	53
1991	53

LEAD REPORT

Mr. OBEY. Let me ask you this. With the recent studies on health and human effects of lead and research that ought to be done in that area, could you supply the Congress that report on lead that addresses those important issues by December 1, 1990?

Dr. RALL. Yes, sir.

ENVIRONMENTAL AND OCCUPATIONAL TRAINING

Mr. OBEY. You provide the only training in government that I know of for environmental and occupational and health personnel. What was the increase in this year's budget for training?

Dr. RALL. The budget for training is level. We had 434 trainees last year, 459 trainees this year and the same number next year. We are initiating a new program, environmental occupational academic medicine, which is to try to encourage those scientists and physicians who are into environmental and occupational medicine,

to form small centers of excellence in their medical school to begin to teach these disciplines to the students. That will help in the long run.

It will take us some years for that to develop, to be useful.

LOWEST BUDGET INCREASE

Mr. OBEY. Just one last point. NIEHS received the lowest update of all of the institutes this year, as I understand. How on earth can that be justified? This is the 20th anniversary of Earth Day coming up. We, again, we have done all kinds of, politicians in every party known to man posing for political pictures, has a real concern for the environment. How do you guys wind up in a caboose?

Mr. RALL. It is a real concern to me. Speaking of Earth Day, if I can invite you all to Earth Tech 1990, which will happen on the Mall April 5 through the 8, which will be a technological exhibit including our balance platform from the University of Cincinnati to see whether kids have lead poisoning and the spirometer from the six-city survey to see if you have lung damage. Stop by our booth and get tested.

Mr. OBEY. Frankly, the way I used to work with asbestos, I don't know if I want to take those tests.

Thank you, Mr. Chairman.

Mr. NATCHER. Mr. Stokes?

LEAD RESEARCH

Mr. STOKES. Thank you, Mr. Chairman.

Dr. Rall, you briefly mentioned Dr. Herb Needleman this morning. I would like to start with some questions about Dr. Needleman's report.

I know you are familiar with the report and his findings. Can you tell us a little bit about his findings about lead?

Dr. RALL. Well, there are two aspects to Dr. Needleman's findings and they are both very important.

He looked at a large number of children. Instead of using blood lead level, which can vary with the recent intake of lead, he used the amount of lead in baby teeth which should provide sort of an averaging of the lead over a period of years. He related then the content of lead in the baby teeth to a series of academic achievements in grade school and teacher evaluations.

He found a smooth dose response curve with the very highest tooth lead level representing children who were slow to learn, who were difficult in school, in attention, disruptive, difficulty in learning to read and so forth. This went from very low levels of tooth lead on up.

When you try to convert this into blood lead level, it is quite clear that his, even his high lead children only had a low to moderate amount in their blood. This was the first study that clearly related failure to learn to blood lead level.

This is very important. It is criticized largely because of its complexity. When all the data were reanalyzed by everybody, it clearly was absolutely correct.

Sort of parenthetically, that was a group with minorities, whites, yuppies, a very mixed group of people which rebutted the previous

objection to these sort of studies where, yes, indeed, the inner city children did not do as well in school but that was because of the problems in the inner city, not because of lead.

This said if you got lead whether you are in the inner city or in the suburbs, you got problems. A similar study in Cincinnati confirmed this.

Most recently Dr. Needleman has gone back and looked at some of those children he studied 6 or 7 years ago and found out how well they did in high school. The results are really very distressing. Those with the highest lead level, still not terribly high, they were six to seven times more likely to have dropped out of high school and never finished and six to seven times more likely to have severe learning disabilities.

The Environmental Defense Fund released figures last week and they are figures that people generally agree with, that as many as three million kids in the United States today have reasonably high blood lead levels. This really is an epidemic.

MONITORING LOW-LEVEL LEAD

Mr. STOKES. How important, Doctor, is regular, long-term monitoring of low-level lead to exposed children?

Dr. RALL. We need to do this not only for the child's sake but to see where the prevention programs are going and how effective they are. Dr. Needleman, and to some extent the Cincinnati group, showed that with very good diets with a child with lead, plenty of calcium, plenty of iron, just a good diet in general, they do seem to be able to recover. With very good parental attention and good environment for the child, they seem to recover.

Interesting, the female children recover better than the male children. No one knows why that is true, but it seems to be true. You want to monitor the children to see how their blood lead level is doing. If it goes up, you have got to intervene and find out what is going on. You need this to know how we are doing in terms of the whole community and the Nation.

Mr STOKES. Are we able, through diet and nutrition, to help these youngsters who are exposed to lead?

Dr. RALL. To some extent, yes. If they are heavily exposed, it won't do any good. If they are lightly exposed, it will help.

Mr. STOKES. Besides children, are there other persons who are especially vulnerable to low-level lead?

Dr. RALL. The Baltimore City Hospital reports—Baltimore City has a reasonably active old house rehabilitation program to try to get rid of lead in some of the older houses. They report that they get very often a worker in that housing rehabilitation program that has lead poisoning from his exposure to the building having the lead removed.

There is a very serious problem there, too. Workers who work on bridges, repainting bridges, they chip off lead paint and get exposed to it. There is a reasonably sized adult occupational group that still is exposed to lead in a serious way.

Mr. STOKES. Is NIEHS doing any type of studies the mobilization of lead from bone? And are you doing any studies in this area that are particularly related to the elderly?

Dr. RALL. We are concerned about the possibility that lead may reduce the calcium in the bones of aging people and increases osteoporosis. In terms of the exposure of the unborn child, the fetus, to lead, we are not sure how much comes from the bones of the mother or how much comes from that amount the mother ingests while she is pregnant.

We have two studies, again with funds this committee helped us obtain, one in primates in Canada, looking at this in monkeys that have lead exposure in the past and are being bred, and two towns in Australia which have different kinds of lead contamination, one older lead contamination and the other current which ought to let us make a comparison between old lead in the bones and current lead being ingested.

We expect in 1 or 2 years or two to have some much better answers.

TOXICOLOGY RESEARCH BENEFITS TO MINORITIES

Mr. STOKES. Can you tell us how toxicology research benefits minorities?

Dr. RALL. We had a good example of that in one of our most recent studies. One substance 1, 3 butadiene had not been tested for carcinogenicity. We found out it was quite carcinogenic in rodents. We retested it and found out it really is a major threat. It is much more carcinogenic than we expected.

Working with some epidemiologists, there is an increase in cancer in exposed occupational groups. The group that is most exposed is composed almost entirely of minority workers. This is a pattern. We begin to see that the minority worker gets what is really the dirtiest job in industry, and those are the people that are most heavily exposed to these chemicals.

Low testing for carcinogenicity of potentially carcinogenic chemicals seems not to be directed to the minorities, ir. many ways it really is because they are the workers that have the dirtiest jobs and get the most exposed.

Mr. STOKES. Are we doing anything in terms of toxicology studies with the historically black colleges and universities?

Dr. RALL. We are doing a little. We would like to do more. We have initiated a program which will let the mid level professors in those colleges work with us for the summer, give them some experience in the sort of work we do and hopefully make it easier for them to apply for NIH grants in the future.

This program is just starting. I think it can be very useful.

Mr. STOKES. I would think that that HBCU's resource would be a good resource to utilize in this area. I am particularly concerned about whether there are very many minorities who are actually involved in toxicology research.

Dr. RALL. Very few, very few.

Mr. STOKES. I would imagine.

Dr. RALL. We hope to increase it this way.

Mr. STOKES. Thank you.

Mr. Chairman, I have a number of other questions, but I will be glad to put them into the record.

Mr. NATCHER. Dr. Rall, we want to thank you and your associates for appearing before our committee at this time on behalf of your budget request for fiscal year 1991. It has been a good hearing, Doctor. Thank you very much.

The committee will now recess until two o'clock.

[Questions for the record and the justifications follow:]

REIMBURSEABLE FUNDING

Mr. Natcher. Insert in the record at this point a table showing the total budget for the institute which identifies the major sources of reimburseable funding and also include a statement on how the 1991 estimate for reimburseable funding was calculated.

Dr. Rall. Yes sir, the following table lists our reimburseable activities.

NIEHS REIMBURSEABLE FUNDING

Source	Description	1990	1991
Environmental Protection Agency	To carry out basic research and training program and worker safety training grant program under Superfund	$36,900,000	$36,900,000
Centers for Disease Control	To carry out toxicological testing activities for the Superfund	3,900,000	3,900,000
NIH-OD	Area grants	175,000	182,000
NIH-OD	Intramural research	121,000	126,000
Miscellaneous	Day care, cafeteria, motor pool, sponsored travel, etc.	380,000	415,000
		41,476,000	41,523,000

These reimburseable activities are all supported by interagency and/or intraagency agreements and the amounts are either known in advance or projected at the same level as the previous year.

NUMBER OF APPLICATIONS RECEIVED

Mr. Natcher. The tables submitted by Dr. Raub's staff indicate that the number of applications submitted to the Environmental Health Sciences Institute has not increased significantly in the last 10 years. This is surprising given the large increase for NIH as a whole and the growing interest in the environment. How do you explain these numbers?

Dr. Rall. Our staff is aware of the lack of significant growth in the number of grant applications assigned to this Institute, which has fluctuated around 400 for the past several years. While we have no firm data to explain this slow growth, there are some factors that contribute to it. First, the NIEHS has not extensively used mechanisms for soliciting grant applications in targeted areas in recent years. The last year in which we did do this, FY 1987, was the year we recorded the most applications. So I believe it is reasonable to assume that by not using such mechanisms, we tend not to get as

large a number of applications as institutes that have used it for targeted programs such as those resulting from Congressional directives, or AIDS initiatives.

The second factor is the overlapping interest of our programs with those of other institutes. For example, both the NINDS and we are interested in effects of toxic agents on the nervous system. Some of the grants submitted in this area may thus be assigned to NINDS rather than NIEHS. The same situation exists in many other areas. Our extramural staff is working with the other institutes and with the Referral Office of the Division of Research Grants, NIH, to clarify the overlap and have applications within our mission assigned here. I do believe there is a high level of interest, and there certainly are many opportunities in the environmental health sciences area, and I think the research community continues to respond to these.

RESEARCH TRAINING INCREASE

Mr. Natcher. The cost of training is about 15% higher in 1990 than you told us last year. What accounts for this substantial increase over your original budget?

Dr. Rall. During its deliberations on the 1990 appropriation, both the House and the Senate, based on its long-term support of research training, provided sufficient funding to raise stipend levels and to increase the number of trainees. This was done for NIH in total, not just for our Institute.

FINANCIAL IMPACT OF NEW CENTER

Mr. Natcher. The overall budget for centers has not been significantly increased in 1990 and would not be increased at all under the President's 1991 proposal. How will the creation of this new center impact on the financial situation of the existing grantees?

Dr. Rall. The new center, to be awarded in FY 1990 and which will specialize in the assessment of agricultural risks, was included in the base carried into the FY 1991 budget request. Our best projections are that it will be necessary to downward negotiate the existing centers by approximately 13.4 percent in FY 1991.

ASBESTOS REMOVAL

Mr. Natcher. We know this is not your direct responsibility but can you tell us how much the Federal government contributes annually towards the cost of asbestos removal?

Dr. Rall. It is my understanding that most of the responsibility rests with the Environmental Protection Agency as a result of the Asbestos School Hazard Abatement Act (ASHAA) of 1984 and, later, the Asbestos Hazard Emergency Response Act (AHERA), which was passed to clarify and expand on ASHAA. A major portion of the program consists of the awarding of grants and loans to schools for asbestos removal. Generally, 25 to 30 percent of the funds are in the form of grants and the remainder are in the form of 20-year, no interest loans. Since 1985 a total of $245 million has been spent on this program.

CHEMICAL TESTING

Mr. Natcher. How many chemicals are you testing each year for toxic risks and how many ideally should you be testing?

Dr. Rall. For the past few years and with the 1991 budget request, we are able to start studies on 10 chemicals for carcinogenicity, 15 chemicals for toxicological characterization, 150 chemicals for mutagenicity, 25 chemicals for developmental and reproductive toxicology, and 10 chemicals for immunotoxicology.

Ideally we should be testing 20 chemicals for carcinogenicity, 30 chemicals for toxicological characterization, 150 chemicals for mutagenicity, 40 chemicals for developmental and reproductive toxicology, and 15 chemicals for immunotoxicology.

Mr. Natcher. What is the annual cost associated with each additional chemical which you begin testing on?

Dr. Rall. It depends on the type of study. The following table should be a meaningful way to disclose the information:

	Cost Per Study *
MUTAGENICITY:	
Drosophilia	$ 9,450
Salmonella	4,425
Cytogenetics	18,100
DEVELOPMENTAL & REPRODUCTIVE (one specie):	
Continuous breeding	160,000
Sperm morphology and vaginal cytology	6,000
Conventional teratology	120,000
Inhalation teratology	200,000
CHEMICAL DISPOSITION (one specie):	115,000
IMMONOTOXICOLOGY PANEL (one specie):	130,000
SUBCHRONIC (Includes studies such as: 14-day, 90-day, clinical chemistry, urinalysis, hematology, and special studies):	
Dosed water	685,000
Dosed feed	635,000
Gavage	710,000
Skin paint	810,000
Inhalation	1,610,000

CHRONIC (Multi-year or lifetime studies; 3 dose levels, blood levels and possibly clinical chemistry):

Dosed water	1,850,000
Dosed feed	1,700,000
Gavage	1,950,000
Skin paint	2,250,000
Inhalation	3,850,000

* Costs include actual contract award, support contracts, and in-house operating costs

FACILITIES

Mr. Natcher. Can you update the Committee on the current situation with respect to the decision to add a new wing onto your facility in North Carolina?

Dr. Rall. We have completed the design phase of the project and have received all of the engineering and architectural clearances. We are prepared to advertise for a construction contract as soon as funds become available.

Mr. Natcher. Have the cost estimates changed from what you described last year?

Dr. Rall. They have changed slightly to reflect increases due to inflation, but otherwise there are no major changes.

Mr. Natcher. Insert in the record at this point a summary of this facility proposal with appropriate budget details.

Dr. Rall. The proposal calls for the addition of two wings to our current facility to house the 300 employees still in the original temporary buildings. One wing will provide modern laboratories to replace the 20 year old ones we are leasing. The other wing will provide replacement office space allowing us to move out of the temporary site and another rental location. The total cost of the project is estimated to be $55 million. Since it costs approximately $4 million per year in rental and other costs associated with maintaining three separate locations, the project would have a payback of approximately 13 years. While not ideal, the two wings could be added one at a time.

MERCURY POISONING

Mr. Conte. Your opening statement mentioned the dangers of mercury in the environment. Mercury has been known as a health hazard for years now. Now you're saying that lakes with acid water seem to have a higher mercury content than non-acidic lakes. What industrial processes might contribute to the release of mercury into the air?

Dr. Rall. There are a number of these. One of the most important is the burning of fossil fuel, especially coal. Mercury is found in small amounts in coal, and burning releases this in the smoke. A number of industrial uses of coal will contribute here--power plants, coke ovens and smelters, kilns, and so forth. Home and industrial heating by coal is a source, too. Chlor alkali plants are sources of mercury. Gold mining by old methods--using mercury to capture gold in an amalgam which is then heated to vaporize the mercury. This is now occurring in parts of South America on a grand scale.

Mr. Conte. Mercury is still used in dental fillings. Is that a potential health danger and are you or the dental institute looking at that? Maybe you ought to put your heads together and find out.

Dr. Rall. This subject has arisen numerous times. The most recent flurry about this probably resulted from a study on sheep just published in the December 1989 FASEB Journal, pages 2641-2647, where it was shown that small amounts of mercury could indeed escape from newly filled teeth and distribute through the sheep's body. However, previously conducted, careful studies in humans do not suggest any severe health problems. Most reports of troubles in people have been anecdotal--no large study has ever turned up anything consistent. I suspect the Dental Institute will be doing some new things here--but they have looked at this several times in the past and nothing has turned up which would suggest a crisis. This may turn out to be something like the asbestos problem. If you have good fillings leave them alone. When you replace old fillings, perhaps you might consider using alternatives.

BIOMARKERS

Mr. Conte. Your budget documents mention that you are going into the field of biomarker research. What are biomarkers and how are they useful?

Dr. Rall. We have been studying biomarkers for many years and they appear to be a useful tool. Among the major issues in much toxicology is how much chemical or toxin actually gets to the place where it can cause ill health, and how do we quantify the adverse actions of this chemical or toxin. Biomarkers will help with both problems. A biomarker is a measurable change in some tissue component made because the chemical has been there and acted. Thus a biomarker of exposure can tell us whether a person has been in contact with a chemical, and whether and how much this chemical has reacted with that person's sensitive systems. An example of a biomarker for exposure would be an adduct, a compound formed from a reaction, between a blood protein and the chemical styrene. To be a biomarker of exposure, the amount of this adduct formed would be proportional to the amount of styrene to which the person was exposed. One of our grantees is successfully doing this work now. A biomarker of effect will tell us if the chemical has exerted an action on that

person which is known to correlate closely with a disease process. An example of an effect biomarker would be oncogenes turned on in cells from the lungs of a smoker. These oncogenes match up with the serious lung damaging properties and cancer caused by smoking. This work is going on now at NIEHS. These biomarkers will make epidemiology more exact and allow us to make better predictions of who will be seriously affected by any environmental exposure.

The use of biomarkers in epidemiology and risk assessment offer an opportunity to understand the underlying mechanisms responsible for epidemiological observations; to identify individuals who might be especially sensitive to the toxic effects of a particular chemical; and to remove some of the uncertainty in the risk assessment process by improving methods for estimating the shape of the dose response curve in the low dose region.

Mr. Conte. How about the PCR reaction - is that helpful for your research?

Dr. Rall. The PCR is an abbreviation for the polymerase chain reaction which is a process whereby small amounts of DNA can be amplified hundreds of thousands of times. This technique is allowing scientists to characterize genetic changes in small numbers of cells thereby obtaining biological data that would not be possible without this technique. The PCR technique is being used extensively in NIEHS and grantee laboratories in a number of ways. For example, we are using it to develop extraordinarily sensitive and specific methods to detect gene mutations in human cells. PCR is also providing a tool to dissect out the critical mechanistic components involved in breast cancer. The bottom line is that the PCR technique may allow us to make early diagnoses of chemically-mediated disease at a time when intervention is more likely to be successful.

TYLENOL RISKS

Mr. Conte. I hear that the active ingredient in Tylenol may cause certain kidney diseases if taken for a long period of time. Can you tell us what is known about this link?

Dr. Rall. Results of our research suggested that individuals who took acetaminophen, the ingredient in Tylenol and many other pain medicines, at least once a day for a year or longer were three times more likely to develop kidney disease than those who did not take pain medicines. This finding is supported by the results of other studies, including some studies in animals. Since ours is the first large, well-controlled, human study to report this risk, other studies are needed to corroborate that acetaminophen causes chronic kidney disease. A chemically related drug, phenacetin, is no longer available in pain medicines because of its link to chronic kidney disease and urologic cancers.

Mr. Conte. Are you looking into other non-steroidal painkillers for potential health risks?

Dr. Rall. Yes. Results from our study also showed that individuals who had been regular users of phenacetin, when it was available in pain medications, were five times more likely than others to develop chronic kidney

disease. We also looked at some of the newer nonsteroidal anti-inflammatory drugs like ibuprofen and indomethacin and found that these may cause kidney disease in some susceptible subgroups of the population such as those who are older or those who also have heart disease. We did not, however, find any kidney disease risk associated with aspirin.

PESTICIDE RISKS

Mr. Conte. In my district there are quite a number of migrant and native farm workers who may come in contact with toxic pesticides. I know you have been active in looking at this problem. Is there anything new you could share with us on the health risks of pesticides?

Dr. Rall. Yes, NIEHS has a substantial program of research on the adverse health effects of pesticides and related agrichemicals. The NIEHS studies range from tracking amounts and types of exposures and using animal models of toxicity, to characterizing metabolites or breakdown products of the chemicals in humans and other living systems, and to determining the chemical structures that predict the biological activity of the materials. Approximately half, or $7.7 million, of the Institute's annual commitment of approximately $15 million to studying the health effects of agricultural chemicals is in grants, primarily overseen by the NIEHS extramural program. Intramural research accounts for another $4 million and contracts, primarily based in the NTP, are valued at $3.2 million.

Pesticides account for only a small fraction of the numerous chemicals in common use, but they pose some of the greatest potential hazards, since they are designed to alter or kill living organisms. Pesticides are spread on growing plants, applied to and injected into the land, and mixed with water for irrigation and sprayed into the air. They pose risks not only to agricultural workers, but to the general population through residues in food crops and through contamination of drinking water. In 1986, the World Health Organization estimated that as many as one million people suffer acute poisoning from pesticides every year, most of them farmers and farm workers. These acute exposures cause an estimated 20,000 deaths a year. Unfortunately, very little is known about the extent of chronic, low-level human exposure to pesticides and its resulting effects. An NIEHS supported study, conducted by the National Research Council in 1984 reviewed available toxicologic data on commercial chemicals, and found that even though pesticides have generally received more extensive testing than other chemicals, serious data gaps remained. Systemic pesticide illness is markedly under-reported. A complete health hazard assessment could be made for only 10% of pesticides.

Of the information that does exist, much comes from NIEHS and the National Toxicology Program administered by NIEHS. For example, in a 1988 JAMA report on the cancer risk of exposure to pesticides for agricultural workers from the Council on Scientific Affairs of the American Medical Association, the Council included the National Toxicology Program as a source for information on 49 of the 53 compounds listed. In addition, this report used 29 entries from the Fourth Annual Report on Carcinogens, a publication of the National Toxicology Program and one of the outlets for information produced through NIEHS studies. Among the recent discoveries are those of the

renal toxicity and carcinogenicity of ochratoxin A, a fungal toxin that may be found in grain, and the carcinogenicity of ethylene thiourea, an ingredient and metabolite of the major class of fungicides in use in the United States, the ethylene bisdithiocarbamates. Ten pesticides are presently under intensive study. The results of long-term studies on the toxicity of methyl bromide, a major contributor to acute neurotoxicity in farm workers, will be made publicly known in April this year.

To help focus attention on the risks to health from exposure to pesticides and to review the results of current research, NIEHS will hold a Symposium on Agricultural Chemical Utilization and Human Health in July, 1990.

INDOOR AIR

Mr. Conte. The quality of indoor air is an item you're beginning to look at. I heard that the new carpet at the E.P.A. headquarters gave off emissions that drove everyone away - it was more toxic than many of the cars they test! What new initiatives are you making in Indoor Air?

Dr. Rall. Although we have no specific initiatives which target indoor air pollution, we have several investigator initiated research projects which contribute a substantial effort to this research area. One such program is the Harvard Six-City Study; another is an epidemiological study of respiratory illness and indoor pollution in Minnesota; yet another study involves the acute respiratory response to industrial chemicals such as used in the rug industry. The objective of this latter study is to understand the mechanisms underlying allergic responses to industrial chemicals. One of the major accomplishments of this study has been to develop a methodology to assess the degree of hyper-reactivity of sensitized airways.

ACID RAIN

Mr. Conte. As you know, I fought long and hard to get research funding for acid rain. Since that time, acid rain has gained national recognition as a risk to health and the environment. Can you tell us anything new about the effects of acid rain?

Dr. Rall. We are continuing to update the research on the health effects of acid rain. In December we held a meeting concerning the possible health effects of metals mobilized from air and soil by acid rain. Acid rain mobilizes a lot of aluminum from soil into surface and well waters, and recent epidemiology in Scotland has suggested that excess aluminum in drinking water may be associated with increased neurological damage in humans, perhaps even Alzheimer's disease. NIEHS has several new grants looking at how water-borne aluminum may affect human health.

Other metals being mobilized by acid rain include lead, mercury, cadmium and arsenic. NIEHS is doing new studies to determine if the primary source of lead transferred from mother to fetus is from the mother's bones or from current ingestion of food, water or air. If it turns out to be water, acid rain may be a serious contributor to fetal and early childhood damage.

In a conference last summer we brought together the best research on mercury and methylmercury in fresh water lakes and their fish. It clearly showed that acidifying lakes leads to more mercury in the water and fish. Methylmercury is a particular hazard to pregnant women and young children. Surprisingly, large numbers of lakes in many states have near-to-dangerous levels of methylmercury in fish and this is getting worse as the lakes become more acid.

The direct effects of acid rain on lungs has been an area of intense NIEHS research for over two decades. Our 6 and 24 Cities Studies, as well as some of our other grantees, are reporting the latest in this work in humans and animals--acid rain does produce definite adverse health effects; there are susceptible populations, such as asthmatic children; acids can potentiate the lung damaging effects of ozone; acids adsorbed to metal containing particles, such as are found in coal and incinerator smokes, are especially hurtful. We agree with the latest NAPAP report interpretation that human health effects of acid rain are clearly evident and that much more research is needed.

NEUROTOXIC CHEMICALS

Mr. Conte. What research is being done to look at the neurobehavioral effects of various chemicals?

Dr. Rall. The National Toxicology Program (NTP) identifies and studies toxic effects of drugs and chemicals, including genetic mutations, carcinogenicity, teratogenicity, and target organ, including the immune system, reproductive system, and nervous system, toxicity. The term "neurotoxicity" is used to describe the potential of an agent to alter the structure or function of the nervous system as defined by indices of neurochemistry, neuropathology, and behavior, including such specific psychological processes as perception, motivation, habituation, learning, and memory. Neurotoxicity can be caused by synthetic chemicals, therapeutic or otherwise, naturally occurring chemical toxicants, ischemia, trauma, and infectious agents. Although its manifestations may change with age, neurotoxicity may occur at any time in the life cycle from gestation through senescence.

The NTP has adopted a sequential or tiered approach to testing for potential neurotoxicity in rodents permitting rejection, acceptance or continuation of the assessment of each tier. Although provisional neurotoxicity assessments in rodents rely primarily on functional observations or measurements, other measures of neurotoxicity, such as neuroanatomical endpoints, are frequently included. The animals in all NTP toxicity studies are closely examined daily for chemical-related changes in demeanor, regardless of the purpose of the study. Changes, when seen, provide clues that more in-depth studies of effects on the nervous system are indicated.

All subchronic toxicity studies and chronic toxicity/carcinogenicity studies include examination of various parts of the nervous system for microscopic changes in structure. The NTP has examined the nervous system in 400 chronic chemical studies. Neurological effects were detected in rats following exposure to ten of these chemicals. In seven of these chemical studies, there were indications of brain tumors. Comparable data have been

obtained for mice. For certain chemicals, the effect of exposure during pregnancy on the functional development of the nervous system of the offspring after birth has been examined. Thus, the NTP is examining the effect of chemicals on the structure and function of the nervous system in rodents in several different test systems.

Mr. Conte. Can you review for us what interaction you have had with the Office of Technology Assessment in regards to neurotoxins?

Dr. Rall. The Office of Technology Assessment (OTA) review of federal research in the field of neurotoxicology included a description of research done by NIEHS and our university-based grantees. The information on NIEHS neurotoxicology research contained in the OTA review came from background materials provided by NIEHS staff and from interviews of NIEHS scientists and management officials. We also commented on early drafts of the OTA review. We found it difficult to arrive at an agreement with OTA staff on what comprises federal research in neurotoxicology. For example, NIEHS funds a substantial body of biomedical research into the neurotoxic effects of environmental lead and other metals. This work is conducted by university-based scientists. We elected to support such research in universities rather than duplicate this pre-existing research capacity at NIEHS. Initially, OTA was reluctant to recognize academic research supported by NIEHS as federal research or relate that research to the mission of our institute. Eventually, this disagreement was resolved satisfactorily.

The NTP participated in a workshop held in May 1989 on Federal Interagency Coordination of Neurotoxicology Research and Regulatory Programs which was co-sponsored by the OTA and the U.S. EPA. As a sequel to that workshop, a steering committee consisting of representatives from the EPA, NCTR, and NIEHS/NTP was named to initiate the formation of an Interagency Committee on Neurotoxicology (ICON). The ICON met in late 1989 and again in February 1990 to discuss items of mutual interest and to exchange information about research goals, test strategies, definitions and other matters where there should be coordination between government agencies. Another meeting of the ICON is scheduled for this April to continue discussions on similar issues in neurotoxicology. The NTP continues to play a key role in these discussions.

RADON DETECTORS

Mr. Conte. Last year you said that you were working with the EPA, Department of Energy and the Cancer Institute to improve the accuracy of radon detectors. Is there any progress to report?

Dr. Rall. Through our Small Business Innovative Research program, the institute has been supporting the development of a canister type radon detector which will be suitable for household use. So far, the company has been able to develop the instrument to meet the Environmental Protection Agency criteria for radon detectors and is now in the process of scheduling an evaluation of this detector. This is an important first step in the development of the device and provides us with an encouraging sign that the need for a sensitive and reliable radon detector may soon be met.

EPA

Mr. Obey. There is much talk of raising the Environmental Protection Agency to a cabinet level. What influence would this have on the NIEHS?

Dr. Rall. The recent moves toward elevating the Environmental Protection Agency to a cabinet-level Department, it seems to me, are in response to the average citizen's heightened awareness of the significance of environmental quality.

At NIEHS we have been working to protect human health from dangerous environmental exposures for over 20 years --- and we will continue to do so. Now we hope that this same increased environmental consciousness that appears to be leading to the elevation of EPA to cabinet rank will also lead to an increased understanding of the absolute dependence of good environmental policy and wise environmental regulation on having solid information. Such an informational base comes only from careful research.

As part of the National Institutes of Health and the Department of Health and Human Services, we at NIEHS who have already developed much data on human health effects of environmental pollutants, look forward to interdepartmental cooperation as equal partners with a new Department of the Environment.

CADMIUM

Mr. Obey. OSHA states in its proposed rule on cadmium that a half a million workers have been exposed to levels of cadmium that exceed the permissible exposure levels and both of the proposed action levels, and that 22-43% of workers exposed to cadmium over a lifetime, will die of lung cancer and 90% of the same workers will suffer kidney disease.

In the February 6, 1990 Federal register comments were made by an unidentified source that I understand to be the Office of Management and Budget on the proposed PELs and action levels for cadmium. (See pages 4075, 4083, 4085, and 4087.) In your opinion, are the conclusions that are being drawn in these comments seriously undermining OSHA's scientific judgment?

Dr. Rall. NIEHS conducts research on the adverse health effects of environmental substances, including metals such as cadmium. The Institute receives requests from Federal regulatory agencies to fill data gaps that would provide a firmer basis for regulatory actions utilizing NIEHS data for more than 200 substances that have been cited in the Federal Register. At present, NIEHS is conducting studies on the toxicity of cadmium oxide and on the teratogenicity of cadmium compounds. The NIEHS role is to conduct research to identify and characterize health hazards and to share the information with governmental agencies and the public; the responsibility for regulatory decisions lies with the regulatory agencies.

LEAD

Mr. Stokes. There seems to be little margin of safety between the lead concentration that many of us come in contact with and the lead concentrations that produce effects like those seen by Needleman and others. Do you have any advice about things the average person can do?

Dr. Rall. There are some things that can be done. First of all, avoid exposures where possible. This includes houses with flaky old lead paint; old houses being renovated; houses with lead, or heavily soldered, water pipes; and areas heavily contaminated with lead, such as heavily traveled older highways or old dumps. Don't drink out of or cook in pottery you aren't sure is lead free, especially older pottery or imports. Don't use leaded gasoline and keep your car air intakes closed in heavy traffic. Do not use lead in hobbies, including solders, ceramics and paints, and stained glass enclosures. Maintain good nutrition. Calcium, iron, and vitamin D are important here. Pregnant women should be especially careful about diet and exposures.

Mr. Stokes. How much is the institute currently spending in this area and how much do you plan to spend in FY 1991? As you will recall, this committee asked you to expand your effort in this area.

Dr. Rall. In FY 1989, NIEHS spent $6.7 million on lead research. In response to the committee's interest, this is being increased to $7.4 million in FY 1990 and $7.7 million in FY 1991.

MINORITIES

Mr. Stokes. Your institute is the home of the National Toxicology Program. What can be done to increase the number of minority researchers in toxicology research and to build a research base in toxicology at minority institutions?

Dr. Rall. It is well recognized that minorities make up only a small proportion of the scientific and engineering professionals. It is also clear that the nation needs a strong "positive contribution" by all groups to remain competitive in world markets. To this end we have undertaken a number of initiatives to increase the number of minority researchers and to build a base of toxicology at minority institutions. We have several efforts going in this area which are beginning to show some promise. First, each of the NIH institutional training grants, which support pre- and post-doctoral students, is required to have in place a plan for recruiting under-represented minorities. This plan is considered in our funding decisions for these grants. In addition we have solicited supplemental applications to our research grant portfolio for the support of minority scientists and minority student scientists. These can range from a few months for summer or off-quarter work to full year support for work in an established environmental health sciences laboratory. We have recently made several such supplements.

The NIEHS has been closely involved with the development of the Historically Black Colleges and Universities/Minority Institutions Consortium focused on hazardous materials and waste management. This is a model for a similar relationship on environmental health sciences research. In addition,

the NIEHS actively participates in the NIH Extramural Associates Program. This program selects scientific faculty and academic administrators from institutions which contribute significantly to the pool of minorities and women in science. The goal of this program is to provide them with on-site information about Federal health-related programs and related grant and contract activities, including those in environmental health sciences.

I am very pleased to report that this year we have initiated a Summer Outreach Program involving science faculty from the NIH Extramural Associates universities and colleges. This pilot program is designed to enhance opportunities for minorities and women to gain summer research experience in the laboratories of some of NIEHS's most prominent scientists. This summer experience should expose minority faculty members, who are often overburdened with teaching and administrative responsibilities and as a result may have had limited research opportunities, to some of the latest technological approaches in such areas as molecular and cellular biology.

In addition, staff are increasingly reaching out to local minority institutions, which are heavily concentrated within a 100-mile radius of the Research Triangle Park, in order to give presentations on their specialized areas of research to college and university students and to participate in ongoing science seminar series. In this outreach effort, particular emphasis is given to universities and colleges involved in the MARC program.

24 CITIES STUDY

Mr. Stokes. You have begun a study of air pollution and human health in 24 cities. Please tell us about this study and the cities involved.

Dr. Rall. The principal objective of this study is to determine the relationship between ambient air concentrations of acidic and five particulate pollutants, and the respiratory health of pre-adolescent children in 24 select communities in the USA and Canada. Twenty of the 24 cities have been studied completely or in part thus far. The first eight were Newton, CT; Monroeville, PA; Dunnville, ONT; Pembroke, ONT; Morehead, KY; Springdale, AR; Livermore, CA; and Hendersonville, TN. The second eight cities were Oak Ridge, TN; Elkins, WV; Charlottesville, VA; Monterey, CA; Jamesville, OH; Penticton, BC; Uniontown, PA; and Simi Valley, CA. The cities to be studied next year are Athens, OH; State College, PA; Blacksburg, VA, and Lemington, ONT; Egbert, ONT; Yorktown, SAS; South Brunswick, NJ; and Hutchinson, KS.

Preliminary findings demonstrate a positive correlation between the level of acid aerosol exposure and bronchitis among the more than 4,000 children examined. Approximately 13,000 children will be examined as a result of this study. Based on findings from the earlier Six Cities Study and 24 Cities Study, it appears that acidity of inhaled particles may be the component most strongly associated with health effects.

GRANTS

Mr. Early. What percentage of new and competing grants will be funded in FY 91?

Dr. Rall. NIEHS plans to fund 21 percent of new and competing grants in FY 1991.

Mr. Early. How does this compare to FY 90 and FY 89?

Dr. Rall. In FY 1990, 24 percent of new and competing grants were funded, and in FY 1989, 27 percent were funded.

Mr. Early. When was the last time your award rate was this low?

Dr. Rall. Twenty one percent is the lowest it has ever been.

Mr. Early. To what payline percentile will you fund under the FY 91 request and how does this compare to the past 2 years?

Dr. Rall. Under the FY 1991 request, we will fund to the 22nd percentile; in 1990 we funded to the 25th; and in 1989 to the 30th.

Mr. Early. What will the downward negotiations be for competing and noncompeting grants for your institute in FY 91, Doctor?

Dr. Rall. In FY 1991, we will downward negotiate 7.3 percent on competing grants and 5.0 percent on noncompeting grants.

CENTERS

Mr. Early. I see that you plan to fund one new center in FY 90. What type of center do you plan to fund?

Dr. Rall. We plan to fund an additional environmental health sciences center to study agricultural chemicals.

Mr. Early. For the record, please provide a list of the types and numbers of centers the NIEHS will fund in FY 90 and FY 91.

Dr. Rall. In FY 1990 and FY 1991 NIEHS will fund 12 environmental health sciences centers and five marine and freshwater biological sciences centers. A list of the center locations follows.

Centers
(dollars in thousands)

	FY 1990	FY 1991
Environmental Health Sciences Centers		
Harvard University	$1,339	$1,339
University of Cincinnati	1,225	1,225
Oregon State University	1,230	1,230
NY University Medical Center	2,284	2,284
Vanderbilt University	1,370	1,370
Mt. Sinai School of Medicine	1,408	1,408
University of Rochester	1,239	1,239
University of California - Berkeley	1,092	1,092
MIT	1,182	1,182
Johns Hopkins University	1,255	1,255
University Med. & Dental - NJ	1,085	1,085
New Center	463	463
Subtotal	15,172	15,172
Marine and Freshwater Biological Sciences Centers		
Duke University	254	254
University of Wisconsin	278	278
University of Connecticut	296	296
Mt. Desert Island Biological Lab	272	272
Oregon State University	278	278
Subtotal	1,378	1,378
Total Centers	16,550	16,550

Mr. Early. You plan to fund the same number of centers in FY 91 as in FY 90, with no increase in funds. What will the downward negotiations be for noncompeting and competing centers?

Dr. Rall. In FY 1990 we will downward negotiate 8.7 percent on noncompeting and competing centers and in FY 1991 we will downward negotiate 13.4 percent.

Mr. Early. Doctor, given our increasing knowledge about potential adverse effects in the area of occupational and environmental health, is there a need to expand the centers program?

Dr. Rall. The Centers program is an extremely important part of our extramural research base. Each Center provides a stable environment for independent yet interdisciplinary research so critical to understanding problems in environmental health. Although the funding for this program has remained level, we have added a mechanism for responding to accidental or unique human chemical exposures by allowing expedited funding of emergency assessments through our Centers. Because of the excellence of research carried out by these Centers and by other NIEHS supported investigators, there are opportunities for new lines of investigation. We have tried to be as creative as possible within the current budget to follow the most promising leads.

CLINICAL RESEARCH

Mr. Early. Doctor, do any of your centers have a "clinical" component and if not, would this be desirable?

Dr. Rall. The inclusion of a clinical activity in our Center grants has been considered on a number of occasions. It is felt that inclusion of a clinical component in these Centers would be a natural outgrowth of the work being supported at these institutes. If adequate funds could be made available, certain Centers could be identified to fulfill what I consider a long overlooked need for research oriented environmental health clinics. In addition to providing a focus for clinical research activities, these clinics would also, hopefully, subject young physicians to experiences dealing with illnesses from environmental exposures.

Mr. Early. To what extent does the NIEHS currently support clinical research?

Dr. Rall. The NIEHS does not support clinical studies from a traditional view point. However, several NIEHS grantees have developed relationships with clinical departments or have clinically-based components of their research. Some examples are: studies on respiratory effects of environmental pollutants in asthmatics, studies on the health consequences of xenobiotic exposure, and studies on the efficacy of specific therapies for reducing bone lead.

Over the years, intramural researchers have also developed collaborative research efforts with a number of clinical investigators throughout the United States and in various foreign countries as well. For example, the Laboratory of Molecular Carcinogenesis is currently collaborating with Dr. Oshimura in Japan to characterize tumor-suppressor genes in lung cancer, renal cancer and endometrial cancers. In addition, scientists from the Laboratory of Pulmonary Pathobiology have joined efforts with the University of North Carolina's Department of Medicine to develop a research program in cystic fibrosis (CF). This program has succeeded in immortalizing bronchial cells from a CF patient, thereby establishing, for the first time, a permanent source of such cells. As a result, investigators will now be able to examine in detail the molecular and biochemical basis of this deadly disease.

The Division of Intramural Research is initiating a new program in clinical research. This program, which is designed to extend basic intramural research efforts into a clinical setting, will be based primarily on research that has definite environmental implications. In addition to providing a clinical setting for the validation of results obtained in basic laboratory research, the program will expand the ability of NIEHS to deal with environmentally-related issues at different levels, including the identification, diagnosis, and treatment of relevant disorders. Furthermore, it will fill a critical public health need by creating a new breed of physicians with clinical research experience in disorders linked to environmental risk factors.

RESEARCH MANPOWER SITUATION

Mr. Early. Doctor, how would you assess the current research manpower situation for areas of interest to your institute?

Dr. Rall. For years, we have recognized that more environmental toxicologists are needed to provide the scientific support required of regulatory legislation such as the Toxic Substances Control Act and the Superfund Act and to carry out research on environmental health issues. To this end, we are making every effort to maximize the effect of our training program dollars to expand pre-doctoral and post-doctoral training in environmental toxicology, and related sciences such as epidemiology and pathology.

RESEARCH CAREER PROGRAM

Mr. Early. How do you use your research career program and what is the focus of this program?

Dr. Rall. We have several initiatives available to develop the research careers of young scientists. Two of these, the physician scientist award and the clinical investigator award, are restricted to medical school and veterinary school graduates who want to train to do independent research in areas relevant to environmental health sciences. Another initiative, the mid-career development award, is available for productive scientists in fields ancillary to environmental health sciences to retrain to do research in environmental toxicology. Our newest initiative is an environmental/occupational medicine academic award to enhance the curriculum in this field at medical centers, ultimately to encourage more physicians to go into clinical or research careers in environmental/occupational medicine.

NEW INTRAMURAL LABORATORIES

Mr. Early. Doctor, last year you indicated that the NIEHS was developing two new intramural laboratories concerned with molecular carcinogenesis and oncogene activation. What is the status of this initiative?

Dr. Rall. The two new laboratories to which you are referring are the Laboratory of Molecular Carcinogenesis in the Division of Intramural Research, and the Laboratory of Molecular Toxicology in the Division of Biometry and Risk Assessment. The overall goal of the Laboratory of Molecular Carcinogenesis is to understand the genes involved in carcinogenesis, including proto-oncogenes, normal cellular genes that are involved in the cellular proliferation process, and tumor suppressor genes, normal cellular genes that are involved with the control or regulation of cell growth, and to elucidate the mechanisms by which environmental substances affect these genes. The major research efforts of the Laboratory of Molecular Carcinogenesis are focused on the cloning and characterizing of tumor suppressor genes; understanding of the interactions between oncogenes and tumor suppressor genes; cloning of transforming genes from human and rodent mesotheliomas; and the understanding of the factors involved in the susceptibility of B6C3F1

mouse to hepatocarcinogenesis, the most frequent mouse target for carcinogens detected in NTP long-term carcinogenesis studies.

The major research efforts of the Laboratory of Molecular Toxicology are determining the biochemical mechanisms responsible for the induction of cancer in laboratory animals by environmental compounds for purposes of quantitative risk analysis; comparing oncogene activation between rodent and human tissues; and developing model systems to examine the various stages in the multi-step process.

Mr. Early. How much has been allocated in your FY 90 and FY 91 budgets for this purpose?

Dr. Rall. The budget allocations for the Laboratory of Molecular Carcinogenesis in FY 1990 and FY 1991 are, approximately $1 million and $1.2 million, respectively. The Laboratory of Molecular Toxicology was allocated $1.1 million in intramural funds and $1.2 million in R & D contract funds in FY 1990, and $1.2 million in intramural funds and $1.3 million in R & D contract funds in FY 1991.

Mr. Early. Could additional funds be used effectively?

Dr. Rall. Additional funds could be used to enhance the research efforts of these laboratories. Recent studies within the Laboratory of Molecular Carcinogenesis have mapped a gene involved in cellular aging and carcinogenesis to human chromosome 1. Additional funding could support further studies to define the precise chromosomal localization of this gene and to clone it. Identification of this senescence gene will lead to important fundamental insights into the processes of aging and cancer formation. Similarly, a tumor suppressor gene for colon cancer is known to be present in human chromosome 5. Approaches to clone this gene could be initiated by first transferring a normal chromosome 5 into colon cancer cells, and then using these suppressed cells to identify the gene responsible for this reversion. Additional funding could provide for support of this project. Funds could also be effectively utilized in the Laboratory of Molecular Toxicology in the detection and identification of activated oncogenes in rodent studies, and to pursue examination of oncogene activation and expression in epidemiologic studies of a variety of human tumors.

PROFESSIONAL JUDGMENT BUDGET

Mr. Early. What was your professional judgment budget for FY 91?

Dr. Rall. Our professional judgment budget for FY 1991 was $292.1 million.

Mr. Early. In which areas does it differ from the request now before the committee? Please provide specific examples for the record.

Dr. Rall. I will provide a mechanism table comparing our professional judgment budget and our current budget request.

FY 1991 Budget
($million)

	Professional Judgment		Budget Request	
	No.	Amount	No.	Amount
Research Grants:				
Res. Projects				
Noncompeting	271	$58.9	271	$54.4
Competing	153	31.5	89	16.9
Subtotal	424	90.4	360	71.3
Centers	19	22.1	17	16.5
Other	52	4.0	35	2.7
Total Grants	505	116.5	412	90.5
Research Training	480	11.4	459	10.6
R & D Contracts	226	75.4	182	59.2
Intramural Research		80.2		67.8
Res. Mgmt. & Support		8.6		7.7
Total, NIEHS		292.1		235.8

NATIONAL TOXICOLOGY PROGRAM

Mr. Early. What are your plans for the National Toxicology Program in FY 90 and FY 91?

Dr. Rall. The NTP will continue to coordinate and strengthen the Department's activities in characterizing the toxicity of chemicals. Plans are to start approximately 10 new carcinogenicity studies, 15 new toxicological characterization studies, 25 developmental or reproductive studies, 150 genetic toxicology studies, 10 immunotoxicity studies, and so forth. The other major thrust will be to continue efforts on the development, evaluation, validation, and application of methodologies that are more rapid, less expensive, or of increased sensitivity and specificity for various toxicological endpoints and the development of alternatives to the use of animals.

GLOBAL CLIMATE CHANGE

Mr. Early. Doctor, will the NIEHS be participating in the "Global Climate Change Initiative"? If so, tell us a little about your institute's role in this initiative, and how much you have allocated in your FY 91 request for this purpose. If not, I would be interested in hearing why, given some of the research missions of your institute.

Dr. Rall. As you know, the President proposed a major global climate research agenda which is reflected in the budget requests for several agencies. The research plan was outlined by the Committee on Earth Sciences, a federal interagency coordinating group convened by the Office of Science and Technology Policy. The plan emphasizes determining the extent and causes of climate change. The National Aeronautics and Space Administration has the principal role in leading this research effort. Somewhat less emphasis will be given to studying the effects of climate change, since scientists are not

yet sure what these changes will be. Still, the Departments of Agriculture and Interior and the EPA will attempt to define the effects on food and forest products and ecological systems. Our role as biomedical researcher is to remain abreast of these research findings and to predict and prevent human health effects. As I mentioned, NIEHS held the first scientific conference on global change and human health and will pursue an active research agenda in this field. We are also working with other NIH institutes to develop a health research agenda for infectious and insect-borne diseases whose occurrence patterns may change in response to global climate change.

HEALTH HAZARDS

Mr. Early. Everyday, we seem to read, or hear about, something in the environment or workplace that is hazardous to one's health. How concerned do we need to be about these stories?

Dr. Rall. Your question is a very good one and more complicated than it appears. There are really two answers, because more than one thing is usually happening when such a story reaches the news media. First of all, we should not and often are not able to ignore the story. The fact that it appears means somebody thinks there's reason to be concerned.

For us as scientists and you as policy makers, when the public is concerned, we must be too. As scientists, it is our job to find out what the story is really about. What do we know about the hazardous agent in question? Do we have solid information already? How do we answer questions if we know only a part of what's going on, as is often the case? Or, if we don't have the kind of detailed information scientists always think is necessary, what information do we need to have to be able to say we should go ahead and use resources to try to get that information? Or to make the judgment that the story is spurious and doesn't warrant studying the agent or the people exposed? If it's spurious, what is our obligation to explain that to the media and the public?

Probably the tougher part of the question is the underlying societal framework that gives the stories a reason for being, and often, in fact, brings them into being. That part of your question is indeed a policy matter that you no doubt wrestle with every day. It goes from the very fundamental questions of responsibility for public health and safety in an economic society to the need for an educated public in the workplace and elsewhere to use and understand the conditions of use for the potent materials that keep our society going.

I guess the short answer to your question might be, 'We need to pay attention in order to find out whether we should be concerned.'

IMPACT OF LACK OF FUNDS IN THE FY 1991 REQUEST

Mr. Early. Will any significant new research initiatives be lost or delayed due to the lack of funds in the FY 1991 request? Please provide, for the record, a list of these along with a brief description and the funding requirements associated with each.

Dr. Rall. There are several areas we would like to pursue if additional funds were available.

In the Division of Intramural Research, we would extend basic intramural research efforts into a clinical setting and fill a critical public health need by creating a new breed of physician with clinical research experience in disorders linked to environmental risk factors. The estimated FY 1991 cost is $500 thousand. We would like to enhance the research efforts of the new Laboratory of Molecular Carcinogenesis in the area of tumor suppressor and senescence gene research. The estimated FY 1991 cost is $300 thousand. We would also expand the transgenic mouse research program. The estimated FY 1991 cost is $225 thousand.

In the Division of Toxicology Research and Testing, we would conduct long-term carcinogenicity studies on 15 chemicals having high production levels or the potential for wide-spread human exposure - $7 million; study important biologic effects other than carcinogenicity, for example, developmental abnormalities, reproductive disorders, abnormalities of the immune system, genetic disease, and neurological impairment for the above chemicals - $2.5 million; learn more about the possible risks to future generations by heritable genetic disorders from exposures to environmental substances - $2.5 million; better determine the extent to which chemicals concentrated in breast milk present a potential risk to nursing babies - $2.5 million; learn more about times of vulnerability for damage to the developing baby before birth - $2.5 million; develop and begin to use transgenic mouse models for evaluation of environmental health problems to permit highly efficient detection of induced genetic changes in either somatic cells where cancer is a concern, or germ cells where the genetic health of the offspring and the quality of life is a concern - $4 million; and develop or modify assays for assessing the toxicity of chemicals that either do not use animals or use fewer numbers of animals - $4 million.

In the Division of Extramural Research, the agricultural workers/farm community is an often neglected segment of the population which could have significant exposure to toxic chemicals. Although the NIEHS has a major research program on the human effects of agricultural chemicals, there is much more research that can be undertaken in order to better protect the health of the agricultural community. Many new research opportunities are emerging in this rapidly developing area. Eight grants could be funded at a cost of $1.6 million.

Human epidemiological and laboratory animal data suggest that certain fiber characteristics are responsible for observed biological effects such as cancer and pulmonary fibrosis resulting from exposures to asbestos. Certain fiber characteristics such as fiber size, length/width ratios, surface chemistries and durability due to chemical composition have been suggested as important factors in their toxicities. This initiative would take three to seven awards at $1.4 million to study this phenomenon in biological models.

Another initiative is on basic mechanistic studies of the long-term and persistent lung pathobiological effects of exposures to environmental agents. Changes in lung biology and the consequences of these changes need to be better understood to better define the hazards of exposures to agents such as

ozone, sulfur dioxide, particles, acids and chemical combinations in smog and other ambient pollution episodes. Some 10 grants are envisioned at a cost of about $1.5 million.

In an effort to increase the level of minority participation, the NIEHS plans to aggressively pursue a new NIH-wide initiative which provides for the administrative supplementation of funded grants. $300,000 is needed for at least 10 supplements.

The NIEHS would like to initiate a Small Grants Program, the main objective of which is to provide a mechanism by which an investigator can mount a study, in a timely manner, on a particular human population exposed to a chemical agent. This program would cost $250,000.

The new Academic Award in Environmental/Occupational Medicine Awards has been developed by the NIEHS in response to the need to create an environmental/occupational medicine focus in medical school curricula. This is seen as an important vehicle for the training of physician scientists in this important area. To institute this program would cost $200,000.

In the Division of Biometry and Risk Assessment, there are intramural and contract research opportunites for activated oncogenes and molecular modeling; mechanisms of action for TCDD and structurally-related compounds; human polymorphisms in drug-metabolizing enzymes; gene-environment interaction in disease risk; and cell proliferation. Approximately $1.2 million would fund the intramural projects and $2.5 million would fund the R & D contracts.

ADDITIONAL FUNDS

Mr. Early. If an increase to your FY 91 budget request is provided, how would you use these additional funds? For the record, please be as specific as possible.

Dr. Rall. My first priority would be to restore the negotiated reduction to noncompeting research project grants in the amount of $2.8 million, and restore the number of competing research project grants to the FY 1990 level plus negotiated reductions at a cost of $3.4 million. I would also restore the negotiated reductions in centers at a cost of $2.6 million. Next I would fund the initiatives mentioned above by adding $10.0 million to R & D contracts, $2.3 million to intramural research, and $5.3 million for research grants.

CLEAN AIR ACT

Mr. Dwyer. As you know, Congressional committees are currently considering a reauthorization of the Clean Air Act. Current law measures the exposure of a hypothetical individual situated at a given distance from the source, for a given number of years. Has NIEHS been consulted by the Environmental Protection Agency on developing a better model to assess risk exposure?

Dr. Rall. NIEHS has been represented in several planning sessions held by EPA to outline a course of action to implement the new authorities of the Clean Air Act. These meetings were internal EPA sessions and were very preliminary in nature. NIEHS staff were invited because of the close professional associations that have developed between EPA and NIEHS in Research Triangle Park. In these sessions, the topic of models of exposure was discussed, including cooperative efforts NIEHS and EPA scientists might pursue to improve these models.

Mr. Dwyer. The proposed legislation may potentially advocate the use of alternative fuels to gasoline. Has the NIEHS examined the toxic levels of the various alternative fuels to determine if they are potentially more toxic than gasoline fumes?

Dr. Rall. We have been following the various proposals for alternative fuels. We share the concern that some of these alternatives might pose potential risks to human health, both at the filling stations where millions of Americans pump their own fuel each day, and in areas of high traffic density where exhaust fumes will accumulate. Scientists on my staff have reviewed the current literature to determine the known toxicity of alternative fuels and their by-products of combustion. We have identified gaps in this knowledge; particularly for methanol, and are developing research protocols to fill these gaps. EPA staff also are aware of this potential problem and a formal request has been made that we conduct additional studies of the toxicity of methanol. We will carry out a study of the effects of long-term, low level exposure to this alternative fuel.

Mr. Dwyer. Does NIEHS operate a central database, with other government agencies, containing information concerning health risks, toxicity, and exposure pathways for certain toxic materials?

Dr. Rall. NIEHS does have information on toxicity and on health risks for the many chemicals we have studied. There are technical reports on the toxic effects of over 350 substances studied in the National Toxicology Program. Not all of these substances were found to be toxic, but reports of studies which find no adverse effects are important. NIEHS prepares the HHS Annual Report of Carcinogens, which lists all substances which are known to cause cancer or can be reasonably considered to cause cancer. And we publish the scientific journal: "Environmental Health Perspectives," which reports on special studies of the risks and effects of environmental substances studied by NIEHS scientists, our grantees, and others. All of these data are used by other federal agencies, physicians, and public health officials in efforts to protect public health and the environment. In addition, we contribute to the

computerized toxicology data base maintained by the National Library of Medicine.

Our Superfund basic research grants program has focused on the development of new and improved methods for the evaluation of exposure pathways for toxic substances escaping from uncontrolled hazardous waste sites. The findings from this research are not yet in a data base, but we will have a conference on exposure pathways at Michigan State University in June of this year.

Mr. Dwyer. What role has the Applied Toxicological Research and Testing program at NIEHS played in the Clean Air Act reauthorization?

Dr. Rall. There has been no direct role. However as I mentioned earlier, we have reviewed the available information on the toxic potential of alternative fuels and are about to begin a study of the chronic toxicity of methanol. In addition, we have reviewed the list of 191 substances included in the proposed air toxins provisions of the Clean Air Act reauthorization bills to determine which have been studied by NIEHS and to determine gaps in our understanding of their toxicology. We found that approximately 40 percent of the 191 substances listed as air toxins have not been studied sufficiently to enable even a crude estimation of risks of long-term low level exposures in communities surrounding facilities releasing these substances.

EXPOSURE TO LEAD AND ASBESTOS

Mr. Dwyer. The NIEHS has been very concerned about the exposure of individuals to toxic environmental agents, such as lead and asbestos. To what extent has the NIEHS been consulted by the Department of Housing and Urban Development to determine exposure levels of lead in our nation's older public housing?

Dr. Rall. NIEHS has assigned a scientist with expertise in the toxicology of lead to the EPA-HUD working group addressing the problem of lead-based paint in substandard dwelling units in the U.S. As you know, research sponsored by NIEHS has highlighted this source of lead poisoning as a dire public health problem.

Mr. Dwyer. What studies are currently underway to determine the various effects of lead exposure to minority children and adults?

Dr. Rall. It is a terribly unfortunate fact that minority children and adults in the U.S. bear a disproportionate burden of adverse health effects from environmental lead exposure. Surveys of lead poisoning in occupational and residential settings clearly demonstrate that less well-educated, poorer, non-white, Americans have many more opportunities for exposure and a higher percentage of these people have elevated levels of lead in their blood and bones. NIEHS-supported researchers are struggling to develop diagnostic tools which are more accurate in detecting lead poisoning, which are less expensive, and which can be used in community screening programs. NIEHS also supports research into improved therapeutics, a most critical need since we now know that lead is toxic at levels that do not respond well to currently available

drugs. We are also looking for better methods to identify and treat women of childbearing age who often transfer lead from their bones and blood to their children during pregnancy.

Mr. Dwyer. There has recently been a great deal of controversy about whether undisturbed, nonflaking asbestos materials should be removed from schools, or simply left in place. What is NIEHS policy for exposure to asbestos and does non-flaking asbestos present a hazard to school children?

Dr. Rall. First, I must point out that NIEHS conducts and supports biomedical research on the human health effects of asbestos and other fibers but we do not have the authority to develop guidelines or regulations necessary to control the risks of exposure to these compounds. Consequently, I cannot offer an NIEHS policy on the removal of asbestos from schools. I can however offer personal judgment I have made previously. In some cases, removal and disposal of non-flaking, stable, asbestos may present health risks to workers and others which are greater that the immediate risks from leaving the asbestos undisturbed. However, nothing in this world is permanent. Some asbestos-containing facilities deteriorate, some are remodeled, sometimes boiler or gas explosions and fires occur. These events can result in the distribution of asbestos fibers to areas where significant exposure to children, teachers and staff take place. Therefore, each situation must be carefully evaluated on its own merits. Common sense, sound professional judgment, and thorough documentation are mandatory. The decision to remove or not to remove asbestos must be made openly so all affected parties know who is responsible for the decision, the facts on which the decision is made, and are in basic agreement with the decision.

LEAD EXPOSURE

Mr. Hoyer. It is becoming more and more clear that there may be no safe lead exposure level. There are occupational, paint and drinking water sources of lead exposure. Can you quantify the relative danger associated with the various sources of lead exposure?

Dr. Rall. Only in a very rough way. There are also marked variations in susceptibility here. In general, the fetus and child are more likely to be damaged by any given exposure. However, the highest exposures are usually occupational, such as lead miners, followed by those related to paint, especially children who eat paint chips or adults burning off many paint layers in a small, unventilated room. In most places, unless a house has lead pipes and the water is acid, lead exposure from drinking water is very small. Generally, food and outdoor dusts are bigger lead sources than drinking water.

Mr. Hoyer. Is there any new data on the impact that lead exposure has had on the cognitive abilities of children and their ability to recover from the deficits caused by lead exposure?

Dr. Rall. We have several ongoing longitudinal studies of lead effects in children. Thus, there will continue to be new data for some time. Some of the most recent reports we have seen suggest that some of these lead-induced deficits may persist for years and even be irreversible. We are developing some more subtle tests of neurological damage to detect less complicated systems than IQ. We are concerned about systems that govern balance and hearing, and fine motor actions. These are certainly affected in children by moderate lead exposures, but we need more studies on such effects at really very low levels of lead. We were encouraged by the findings that extra parental and school attention and support might ameliorate some of the early lead damages we observed. We need to know more about that.

Mr. Hoyer. Could NIEHS outline the parameters of the problem for the committee with respect to any important variations in the prevalence of dangerous lead exposures by geographic, socio-economic, or any other important variant that sheds light on how this problem ought to be attacked?

Dr. Rall. Most dangerous exposures of children to lead today are from paint and dust. Neighborhoods with older houses or near older highways generally have the highest lead contaminations. This does not automatically translate into inner city, or older city, or lower socioeconomic class problems. Indeed, one of our studies is on suburban Boston children, and we find lead exposure there. One of our studies shows that children with pre- and postnatal, low-to-moderate lead exposures do respond positively to extra attention from parents and teachers. This was in terms of only some of the lead induced deficits but does suggest possible actions to be taken.

Mr. Hoyer. Does lead exposure have different affects when there are controls for gender, race or socio-economic status?

Dr. Rall. For some effects, apparently yes. Males in both animals and humans seem to be more susceptible, but it is not clear if this is related to gender or behavior. As far as race and socioeconomic status, the relationship

is unclear. Although the hypertensive effects of lead may be seen more often in blacks, all else is apparently equal. But, what race is most likely to live in older homes and near older, heavily trafficked highways? As I mentioned before, extra parental and school attention seems to blunt some of the effects of fetal and perinatal lead exposures. Is this extra attention more likely in higher or lower socioeconomic class homes?

SHELLFISH

Mr. Hoyer. As a Maryland legislator, I am very concerned about the Chesapeake Bay and the impact that pollution has had on the harvests from the Bay in recent years. Does NIEHS have any involvement in the area of environmental hazards that ultimately impact on humans as a result of their consumption of shell or other fish foods and if so, could you elaborate on your role, and any information you may be able to share with the committee regarding this apparently serious and growing problem?

Dr. Rall. NIEHS has had an interest in the accumulation of pollutants in fish and other seafood for many years. We have a small intramural program which for years has studied the processes and mechanisms of accumulation and excretion of carcinogens, metals, and pesticides and PCBs in things like flounder, oysters, clams, lobsters, killifish, and shark. We also have a continuing Marine and Freshwater Centers grants program with several projects in this area and in the area of fish as environmental monitors or disease models. In September 1988, we had a conference at NIEHS on some of these topics in response to the findings of cancers in increasing numbers in fish and shellfish along both east and west coasts of the U.S. as well as other places in the world. There were many questions, but the major one was--are these fish dangerous to eat? Some of the bottom lines of that conference were that for most pollutants, except metals, fish were poor accumulators, while shellfish were much better; parts of fish and shellfish, such as the liver, kidney, and bile of most species, had large amounts of pollutants, but most of the pollutant-rich parts were not consumed by humans; and that fish were serving most likely as an early warning system for the presence of dangerous pollutants and carcinogens in both fresh and ocean water. The proceedings of that NIEHS conference are being published in our journal, Environmental Health Perspectives, in September 1990.

Last summer we had a conference on mercury and methylmercury accumulation in fish in fresh water. Metals accumulate in ocean and fresh water animals in general proportion to their age, size, and predator status and the degree of water contamination with the metal. Fish can accumulate enough of some metals to be hazardous to health--mercury and cadmium are special cases here. The NIEHS role here is to focus on the human health aspects and on environmental contaminants--not on bacteria and viruses. We are members of a number of liaison committees on the general problems of food contamination--and fish and seafood are considered in many of these meetings. Our Superfund grant program has some small efforts using fish as markers for dump leakages. This has so far confirmed previous findings that fish can serve as early warning systems for a number of chemicals in water.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

FY 1991 Budget

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NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

For carrying out section 301 and title IV of the Public Health Service Act with respect to environmental health sciences, [$233,264,000] *$235,792,000*.

(Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 1990.)

NATIONAL INSTITUTES OF HEALTH

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

Amounts Available for Obligation 1/

	1989 Actual	1990 Appropriation	1991 Estimate
Appropriation	$226,168,000	$233,264,000	$235,792,000
Enacted administrative reduction	-2,714,000	-788,000	---
Sequester Order	---	-3,242,000	---
Subtotal, adjusted appropriation	223,454,000	229,234,000	235,792,000
Real transfer to: Health Resources and Services Administration for AZT grants	-51,000	---	---
Comparative transfers to:			
Division of Research Resources for RCMIs	-7,000	---	---
FIC Passport Agency	-1,000	-1,000	---
Comparative transfer from:			
Office of the Director, NIH for FTE increase	+291,000	---	---
Subtotal, adjusted budget authority	223,686,000	229,233,000	235,792,000
Unobligated balance, lapsing	-94,000	---	---
Total, Obligations	223,592,000	229,233,000	235,792,000

1/ Excludes the following amounts for reimbursable activities carried out under this account: 1989 -- $27,706,000; 1990 -- $41,476,000; 1991 -- $41,523,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Budget Mechanism
(Dollars in thousands)

Research Grants	1989 Actual No.	1989 Actual Amount	1990 1/ Appropriation No.	1990 1/ Appropriation Amount	1991 Estimate No.	1991 Estimate Amount
Research Projects:						
Noncompeting	259	$45,311	259	$48,687	271	$53,753
Administrative supplementals	(17)	1,648	(10)	492	(10)	627
Competing:						
Renewal	49	11,312	55	12,280	49	11,255
New	48	6,523	44	6,095	40	5,595
Supplementals	3	289				
Subtotal, competing	100	18,124	99	18,375	89	16,850
Subtotal, research projects	359	65,083	358	67,554	360	71,230
Research Centers	16	16,223	17	16,550	17	16,550
Other Research:						
Research career programs	21	1,367	22	1,485	22	1,485
Minority biomed. res. support	--	403	--	404	--	438
Other research related	25	780	13	766	13	766
Subtotal, other research	46	2,550	35	2,655	35	2,689
Total, Research Grants	421	83,856	410	86,759	412	90,469
Training						
Individual awards:						
Noncompeting	19	474	25	603	27	674
Competing:						
New	16	389	14	344	12	273
Supplementals		15				
Subtotal, individ	35	878	39	947	39	947

Institutional awards:						
Noncompeting	356	7,348	310	6,913	377	8,501
Competing:						
Renewal	38	626	83	2,138	43	1,138
New	5	113	27	588	--	--
Supplementals		108	--	--	--	--
Subtotal, inst	399	8,195	420	9,639	420	9,639
Total, training	434	9,073	459	10,586	459	10,586
Research & Development Contracts	180	61,111	182	59,437	182	59,164
	FTEs		FTEs		FTEs	
Intramural Research	581	62,157	586	64,678	594	67,840
Research Management and Support	86	7,489	87	7,279	89	7,733
Extramural Construction		--		494		--
Total, NIEHS	667	223,686	673	229,233	683	235,792
HIV/AIDS	(7)	(4,197)	(7)	(4,291)	(8)	(4,580)

1/ Includes approximately $494,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

CROSSWALK - 1989 Actual

(Dollars in thousands)

PROGRAM ACTIVITY	MECHANISM								
	Research Grants			Training Programs		Research and Development Contracts	Intramural Research	Research Management and Support	Total
	Research Projects	Research Centers	Other Research	Individual	Institutional				
Biological response to environmental agents	$55,934	$25	$2,109						$58,068
Applied toxicological research and testing	4,139		272			$56,659			61,070
Biometry and risk estimation	5,010		169			4,452			9,631
Resource and manpower development		16,198		$878	$8,195				25,271
Intramural research							$62,157		62,157
Research management and support								$7,489	7,489
Total	65,083	16,223	2,550	878	8,195	61,111	62,157	7,489	223,686

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

CROSSWALK - 1990 Appropriation 1/

(Dollars in thousands)

PROGRAM ACTIVITY	MECHANISM									
	Research Grants			Training Programs		Research and Development Contracts	Intramural Research	Research Management and Support	Extramural Construction	Total
	Research Projects	Research Centers	Other Research	Individual	Institutional					
Biological response to environmental agents	$57,827		$1,956							$59,783
Applied toxicological research and testing	4,992		151			$54,937				60,080
Biometry and risk estimation	4,735		548			4,500				9,783
Resource and manpower development		$16,550		$947	$9,639					27,136
Intramural research							$64,678			64,678
Research management and support								$7,279		7,279
Extramural construction									$496	496
Total	67,554	16,550	2,655	947	9,639	59,437	64,678	7,279	496	229,233

1/ Includes approximately $496,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

CROSSWALK - 1991 Estimate

(Dollars in thousands)

PROGRAM ACTIVITY	MECHANISM								
	Research Grants			Training Programs		Research and Development	Intramural	Research Management	
	Research Projects	Research Centers	Other Research	Individual	Institutional	Contracts	Research	and Support	Total
Biological response to environmental agents	$60,039		$1,985						$62,024
Applied toxicological research and testing	6,224		154			$54,663			61,041
Biometry and risk estimation	4,967		550			4,501			10,018
Resource and manpower development		$16,550		$947	$9,639				27,136
Intramural research							$67,840		67,840
Research management and support								$7,733	7,733
Total	71,230	16,550	2,689	947	9,639	59,166	67,840	7,733	235,792

National Institute of Environmental Health Sciences

Summary of Changes

1990 Estimated budget authority	$229,233,000
1991 Estimated budget authority	235,792,000
Net change	+6,559,000

	1990 Current Estimate Base		Change from Base	
	Pos. (FTEs)	Amount	Pos. (FTEs)	Budget Authority
Changes:				
A. Built-in:				
1. Annualization of 1990 pay increases		$30,483,000		$+288,000
2. Within grade increases		30,483,000		+231,000
3. One extra day of pay		30,483,000		+115,000
4. 1991 pay increase				+940,000
4. Increased cost of centrally furnished services		2,192,000		+269,000
5. Federal Employee Compensation Fund		133,000		+4,000
6. Increased cost of unemployment compensation		63,000		+2,000
7. Increased cost of Federal Telecommunications System		35,000		+1,000
8. Increased cost of laboratory supplies, materials, and other expenses		39,586,000		+1,338,000
9. DHHS Working Capital Fund		336,000		-16,000
Subtotal				+3,172,000
	No.	Amount	No.	Amount
B. Program:				
1. Research projects grants:				
a. Noncompeting	259	49,179,000	+12	+5,201,000
b. Competing	99	18,375,000	-10	-1,525,000
Total	358	67,554,000	+2	+3,676,000
2. Other research		2,655,000		+34,000
3. Research and development contracts		59,437,000		-273,000
4. Intramural research	(586)	64,678,000	(+8)	+415,000

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Summary of Changes, continued

	1990 Estimate Base No.	1990 Estimate Base Amount	Change from Base No.	Change from Base Amount
5. Research management and support	(87)	7,279,000	(+2)	+29,000
6. Extramural construction		494,000		-494,000
Subtotal, program				+3,387,000
Total changes				+6,559,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Budget Authority by Activity
(Dollars in thousands)

	1989 Actual		1990 Appropriation 1/		1991 Estimate	
	FTEs	Amount	FTEs	Amount	FTEs	Amount
Biological response to environmental agents	--	58,062	--	59,783	--	62,024
Applied toxicological research and testing	--	61,[illegible]	--	60,080	--	61,041
Biometry and risk estimation	--	9,631	--	9,783	--	10,018
Resource and manpower development	--	25,271	--	27,136	--	27,136
Intramural research	581	62,099	586	64,678	594	67,840
Research management and support	86	7,460	87	7,279	89	7,733
Extramural construction	--	---	--	494	--	---
Total obligations	667	223,592	673	229,233	683	235,792
Unobligated balance lapsing	--	94	--	---	--	---
Total Budget Authority	667	223,686	673	229,233	683	235,792
HIV/AIDS	(7)	(4,197)	(7)	(4,291)	(8)	(4,580)

1/ Includes approximately $494,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

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NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Budget Authority by Object

	1990 Appropriation	1991 Estimate	Increase or Decrease
Total number of full-time permanent positions	517	522	+5
Total compensable workyears:			
Full-time employment	726	736	+10
Full-time equivalent of overtime and holiday hours	6	6	---
Average ES salary	$92,450.00	$95,685.75	+$3,235.75
Average GM/GS grade	9.66	9.66	---
Average GM/GS salary	35,870.56	37,126.03	+1,255.47
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	58,919.71	60,981.90	+2,062.19
Average salary of ungraded positions	25,730.65	26,631.22	+900.57
Personnel compensation:			
Full-time permanent	$18,358,000	$19,578,000	+$1,220,000
Other than full-time permanent	5,709,000	6,033,000	+324,000
Other personnel compensation	561,000	583,000	+22,000
Special personnel service payments	1,421,000	1,476,000	+55,000
Total personnel compensation	26,049,000	27,670,000	+1,621,000

	1990 Appropriation	1991 Estimate	Increase or Decrease
Personnel benefits	4,434,000	4,736,000	+302,000
Benefits for former personnel	25,000	25,000	---
Travel and transportation of persons	921,000	976,000	+55,000
Transportation of things	93,000	94,000	+1,000
Rent, communications, and utilities	6,437,000	6,604,000	+167,000
Printing and reproduction	300,000	308,000	+8,000
Other services:			
Project contracts	59,437,000	59,164,000	-273,000
Centrally furnished services	1,888,000	2,130,000	+242,000
Standard level user's charge	304,000	304,000	---
Other	17,347,000	18,079,000	+732,000
Supplies and materials	7,729,000	7,980,000	+251,000
Equipment	6,430,000	6,667,000	+237,000
Grants, subsidies & contributions	97,839,000	101,055,000	+3,216,000
Interest	---	---	---
Total budget authority by object	229,233,000	235,792,000	+6,559,000

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NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Significant Item in House Appropriations Committee Report

Item	Action taken or to be taken
1990 House Report	
1. "The Committee continues to be concerned about the problem of lead exposure to children. Within additional resources provided, the Committee encourages the Institute to support additional research into the effect of lead poisoning and its treatment." (House Report No. 101-172, p. 76)	1. NIEHS continues to give high priority to basic research into the diagnosis, treatment and prevention of childhood lead poisoning. Emphasis has been placed on finding methods to detect elevated levels of lead in blood and bones for recent and long-term exposure assessment, and on assuring that as children are treated for lead poisoning, lead is released from body stores gradually and does not further damage the kidneys and nervous system. It is clear from NIEHS-supported research that lead poisoning will continue to be among the most serious environmental illnesses affecting American children, particularly from poor children in eastern cities and in certain rural areas.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Significant Items in Senate Appropriations Committee Report

Items	Action taken or to be taken
1990 Senate Report	
1. "The Committee is concerned that ozone depletion in the upper atmosphere and global warming are alarming international environmental problems which carry with them new threats to public health and, therefore, directs NIEHS to establish new initiatives in these areas." (Senate Report No. 101-127, p. 142)	1. NIEHS has identified additional research needed to prevent potential adverse health effects from loss of ozone and from global warming. Loss of upper atmosphere ozone permits an increase in ultraviolet radiation reaching the earth's surface. This "extra" ultraviolet may depress human immune response, increasing susceptibility to infectious diseases, and increasing skin cancers. It is also linked to an increase in cataracts. Human health has been missing from reports on elements projected to be affected by an increase in global temperature. NIEHS sponsored a conference on Global Climate Change and Human Health, the first to address the question. A number of potential impacts were identified, including: a growing range for certain potentially fatal insect-borne infectious diseases that have not been common in the United States; the effects on human health of exposure to emissions from alternative fuels and to substitutes for CFCs; and the effects on nutrition and heat responses of changed regional climates.

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Significant Items, Continued

2. "NIEHS/NIH is directed to initiate a comprehensive research program to address all aspects of toxicology of agricultural chemicals, including synthetic and naturally occurring chemicals and their environmental metabolites. This program should include assessment of carcinogenicity, mutagenicity, neurotoxicity, and assessment of reproductive toxicity. NIEHS is also directed to coordinate a Federal research initiative on agricultural chemical toxicity through the National Toxicology Program, through its extramural grants and contracts program, and through the development of a university-based research center or contract to conduct research in the national interest on the toxicity of agricultural chemicals." (Senate Report 101-127, p. 143)

2. NIEHS held a conference of leading experts on agricultural chemical uses and on the biomedical effects of exposure to agrichemicals to determine research gaps and priorities. Based on their advice, NIEHS has has established a program of basic toxicologic and biochemical research in order to develop a better understanding of the extent of the risks posed by exposure to agrichemicals for production workers, users, and consumers of treated commodities. Efforts are under way at NIEHS to fund a university-based, centralized research program on agricultural chemicals.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1990 Amount Authorized	1990 Appropriation	1991 Amount Authorized	1991 Budget Estimate
Research and Investigation.....	Section 301	42§241	Indefinite	$218,647,000	Indefinite	$225,206,000
National Institute of Environmental Health Sciences.....	Section 463	42§285	Indefinite		Indefinite	
National Research Service Awards.....	Section 489	42§288	Such Sums as Necessary 1/	10,586,000	Authorizing Legislation to be Requested	10,586,000
Total Budget Authority				229,233,000		235,792,000

1/ This training authority is shared with other research training programs of the National Institutes of Health and the Alcohol, Drug Abuse, and Mental Health Administration.

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NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Appropriations History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1982	96,851,000 2/	111,256,000	111,870,000	106,270,000
1983	157,448,000 3/	162,695,000	166,040,000	164,863,000
1984	165,884,000	173,627,000 4/	172,374,000 4/	179,802,000
1985	183,755,000	189,437,000 5/	191,908,000	194,056,000
1986	183,755,000	188,319,000 6/	198,3[illegible],000	197,478,000
1986 Sequester				-8,492,000
1987	187,995,000	209,872,000	208,067,000	209,294,000
1988	198,431,000	225,724,000 7/	220,709,000	215,666,000
1989	218,471,000 8/	216,985,000 9/	223,168,000	223,454,000 10/
1990	226,471,000 11/	232,479,000	234,048,000	229,234,000 12/
1990 Sequester				-3,242,000
1991	235,792,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Reflects the September amendment; the original request was $110,058,000.

3/ Includes $48,165,000 to support the Bioassay Program transferred from the National Cancer Institute.

4/ Excludes $5,319,000 in NRSA training programs not considered.

5/ Excludes $5,922,000 in NRSA training programs not considered.

6/ Excludes $8,502,000 in NRSA training programs not considered.

7/ The House allowance consolidated AIDS funding ($4,091,000) in the Office of Assistant Secretary for Health.

8/ The 1989 request excludes funding for AIDS research and education ($4,234,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

9/ Excludes $9,183,000 in NRSA training programs not considered.

10/ Excludes $2,714,000 administrative reduction.

11/ The 1990 request excludes funds for the National HIV program ($4,377,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

12/ Excludes $788,000 enacted administrative reduction.

Justification

National Institute of Environmental Health Sciences

	1990 Appropriation		1991 Estimate		Increase or Decrease	
	FTE	BA	FTE	BA	FTE	BA
TOTAL....	673	$229,233,000	683	$235,792,000	+10	+$6,559,000
HIV/AIDS.	(7)	(4,291,000)	(8)	(4,580,000)	(+1)	(+289,000)

General Statement

The National Institute of Environmental Health Sciences (NIEHS) is the primary focus of basic environmental health sciences research for the National Institutes of Health. NIEHS, established in 1966, develops the scientific information needed to identify and prevent environmentally-related diseases and to protect public health through basic and applied research programs. The Institute supports research and training to further our understanding of how agents in the environment affect human health, and to provide sound scientific information on substances potentially toxic to human health that may enter the environment.

In a period of accelerating changes in our environment, NIEHS' 25 years of experience in unravelling the relationships between the environment and human health and disease is critically important to protecting public health now and as we move into the 21st Century. The question posed in NIEHS research asks how chemical, physical, and biological agents in our surroundings affect human health. The goal of NIEHS-supported training programs is to provide well-trained environmental health scientists who are prepared to address that question appropriately and to identify, ameliorate, and prevent adverse health effects of environmental agents.

NIEHS studies have identified the nature and scope of the human health threats posed by asbestos and lead; determined, in animal studies, that survivors of exposure to methyl isocyanate, the killer gas of Bhopal, may have long-lasting lung effects; and found that some of the proposed substitutes for the ozone-destroying chlorofluorocarbons may not be safe for human health, to cite a few examples.

NIEHS laboratories identify and characterize potentially harmful agents and their health effects, using the most advanced tools of molecular biology and study designs that are the world standard for both short-term and long-term chronic toxicity and carcinogenicity evaluation. The effects of toxic agents may appear as neurological and behavioral disorders, respiratory disease, cardiovascular disease, metabolic and endocrine disorders, kidney

dysfunction, cancer, genetic damage, impaired reproduction, birth defects, developmental disabilities, and immune disorders, among others.

Identifying the changes that occur in biological systems as a result of exposures, using models that follow the route of human exposure, is one important facet of NIEHS research. Developing methods to identify who has been exposed to toxic agents in the environment, developing methods to determine the levels of exposure in the general population and for individuals within the population, and developing methods that can help identify those most susceptible to adverse effects of the agents are also important aims of the Institute's research.

Overall Budget Policy

The 1991 budget request for NIEHS favors basic research and totals $235,792,000, an increase of $6,559,000 over the 1990 comparable level. Sixty-eight percent of the budget request would support research grant, training, and contract activities, and 32 percent of the request would support intramural research and research management activities. AIDS-related research funds of $4,580,000 are included.

In 1991, the budget request would fund 89 competing research project grants at an average cost of $189,300, and an award rate of 21.3 percent. This would allow funding through the 25th percentile. The average cost is 2.0 percent greater than 1990. The request would support 271 noncompeting research project grants at an average cost of $198,300. The average cost of noncompeting grants is 5.5 percent more than in 1990.

Twelve environmental health sciences centers and five marine and freshwater biomedical sciences centers would receive $16,550,000 in support from this request, about the same as in 1990. Other research grants would receive $2,689,000 in this budget.

The 1991 request would support 459 research trainees for $10,586,000, the same as in 1990.

Contracts to support research and development in toxicity testing and test development, in risk estimation methods, and for other scientific problems in environmental health are projected at $59,154,000. Approximately 182 contracts would be included, the same as in 1990.

Intramural research funds of $67,840,000 and research and management funds of $7,733,000 are requested.

Program Accomplishments

The techniques of molecular biology are maturing as tools for research important to the mission of the National Institute of Environmental Health Sciences. From the intricacies of the genetic code to the pathways for cell-to-cell communication, these new tools are improving scientists' ability to identify the environmental agents that affect human health in many different ways: the health of children and our ability to reproduce, our chances of having cancers and nerve disorders, and how well our immune systems function. Applying these new tools has led to some of the most promising program accomplishments NIEHS is reporting this year.

NIEHS scientists, studying those genes thought to be associated with cancer, have identified two new oncogenes: one that is activated in human mesothelioma, a cancer due to asbestos exposure, and another oncogene that is found in a specific group of human lung cancers. Investigators have mapped to human chromosome 1 a tumor suppressor/ cell senescence gene, involved in growth regulation processes.

Using a new technique to introduce individual chromosomes found in normal cells into cancer cells, scientists have shown that chromosome 11 can suppress a number of malignant tumors including cervical cancer, Wilms' tumor, rhabdomyosarcoma, and lung adenocarcinoma in cell cultures. These insights into the function of segments of the genetic code have promise in the search for treatments for these diseases.

Long-term human epidemiological studies continue to produce valuable information. Studies of children exposed to lead and mercury suggest there may be no threshold for some subtle effects of these metals in humans. Studies of the short and long-term effects of air contaminants have shown that acid aerosols are key players in lung damage from air pollution, and that mixtures of pollutants-- sulfur and nitrogen oxides plus ozone that make the acids-- are more damaging to lungs than single pollutant exposures.

Risk factors for end stage renal disease are being identified in a large epidemiologic study. NIEHS epidemiologists have reported an association between long-term, daily use of acetaminophen and risk of kidney disease. Analysis of data on the use of other drugs and exposure to solvents is under way. In a study of great public health significance, the consequences of exposure to high levels of radon in residences is being carefully explored. This study also addresses the important question of risks due to a combination of tobacco smoke and radon exposure.

Biomarkers of exposure to environmental agents in DNA and blood proteins have been developed, and a biological system has been established in which the genetic changes of a single DNA adduct (addition product of DNA and a xenobiotic agent) can be determined in bacteria or mammalian cells.

New methods for analyses of data are being used to seek the common elements in biological changes caused by environmental agents, with the goal of predicting which agents may be of concern for human health.

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Scientists working on why the Human Immunodeficiency Virus changes so rapidly have identified four classes of mutations and the locations in the genetic code where the mistakes most often occur in the virus that causes Acquired Immune Deficiency Syndrome or AIDS. By identifying the mistake-prone areas of the code for the enzyme responsible for making copies of the virus, these studies may lead to better drugs that target the reverse transcriptase of the retrovirus.

A collaborative project has generated an epithelial cell line from the airways of a cystic fibrosis patient that shows the abnormalities typical of cystic fibrosis. This cell line makes it possible to study molecular mechanisms within the cells, to look for complementary genes that may correct the abnormalities of cystic fibrosis, and to seek effective new treatments for the disease.

Hormones and agents that act like hormones in development and disease have generated increasing interest. NIEHS scientists recently demonstrated that estrogen can affect cells that have no known estrogen receptors early in cell development, perhaps through growth factors involved in imprinting genital tract genes. They concluded that estrogen can misprogram the expression of hormone-induced genes in the male genital tract, an activity that may account for the proposed association between early exposure to estrogen and adult prostatic cancer.

In studies of three nickel compounds commonly found in the workplace, investigators are relating carcinogenic results to changes in the immune system and tissue distribution of nickel, and comparing the toxicities of water-soluble and insoluble nickel compounds in rodent models.

Studies of the comparative metabolism of chemicals in human and animal tissues have produced similar metabolic profiles, with some qualitative and quantitative differences between the species. Study of the changes in metabolism that accompany aging and the relationship of these changes to the toxicity of environmental agents is continuing. In related efforts, cultured human cells have been made 10 to 1000 times more sensitive to two known mutagens by genetic manipulation. A mouse cell line has been altered to enable it to activate carcinogens more readily. Increased metabolic capability in these replicating cell lines will allow low-dose experiments in cultured cells.

Studies of the effects of chemicals on the immune system have included the pesticide Aldicarb, the AIDS drug 2',3'-dideoxyadenosine, and the anabolic steroid oxymetholone. Methods were developed for using B-cell maturation as an in vitro model to study the cellular and molecular events in chemical-induced immunotoxicity. A mixture of chemicals commonly found near toxic waste dumps caused immune system changes including lowered resistance to infection in experimental animals that drank the water mixture.

Meanwhile, work is continuing on developing alternatives to mammalian models for study. The models currently being examined include frog eggs, earthworms, and fish.

AIDS Research Program

NIEHS AIDS Program

The National Institute of Environmental Health Sciences has brought its skills and knowledge in a variety of basic sciences to bear on the multiple challenges to public health posed by Acquired Immune Deficiency Syndrome (AIDS). Since NIEHS has one of the largest mutagenesis programs in the Federal government, it logically follows that NIEHS scientists are studying the hypervariability of Human Immunodeficiency Virus (HIV) and the body's response to the virus. In conducting one of the government's largest testing programs for potential health effects of environmental agents, NIEHS scientists are overseeing studies of the toxicity of drugs used to treat the disease.

Recent Research Accomplishments

NIEHS is involved in characterizing the toxicity of chemicals used to treat AIDS patients and those with AIDS-Related Complex (ARC), part of the search for treatments that will do more good than harm in patients. NIEHS scientists are testing, in animals, an array of drugs and drug combinations currently being tested by others in patients for potential side effects. The studies measure general toxicity and target organ lesions; toxicity to the nervous system, bone marrow, and blood forming system; reproductive toxicity and chemically induced birth defects.

These questions become more important as people exposed to the virus may be treated for much longer periods. This is especially true for newborns from infected mothers. There is evidence in the animal model of an extensive range of birth defects after in-utero exposure to DDC (dideoxycytidine), suggesting the need for caution in using certain anti-AIDS drugs in women who are or may become pregnant.

In toxicity studies requested by the Food and Drug Administration, pentamidine, the drug used against a pneumocystis pneumonia that often afflicts AIDS patients, inhibited one of the interleukins. Another drug used to treat AIDS patients, DDA (dideoxyadenosine), suppresses antibody response, specifically the B lymphocyte, after antigenic stimulation; it was found to damage the kidney also. DDI (dideoxyinosine), also being used for AIDS therapy, inhibited antibody responses as well, but produced no nephrotoxicity.

One of the problems doctors face in treating AIDS patients is managing opportunistic infections that are the cause of most AIDS-related deaths. These are infections by agents that seldom cause trouble for normal adult immune systems. NIEHS scientists have applied molecular biology techniques developed in studies of estrogen-like chemicals to examine the inability of AIDS patients to fight such secondary infections. A major antibacterial protein in white blood cells, lactoferrin, may be one of the keys. NIEHS investigators have cloned the lactoferrin gene and have developed molecular probes to study the role of lactoferrin in secondary disease among both AIDS and leukemia patients.

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Research Plans

The rapidly mutating HIV does not proofread its own RNA:DNA copying very well, making it difficult to study the virus' molecular biology and develop treatments. HIV mutates its genetic information to escape the defense systems in infected individuals. NIEHS scientists, applying their skills in molecular mutagenesis to examine the nature of the copying errors, have found that the mutations may be the result of errors made by the HIV enzyme that makes new copies of viral genetic information. Current NIEHS studies of how this enzyme makes errors may provide useful information for designing drugs and vaccines to treat or prevent this disease.

National Institute of Environmental Health Sciences

Biological Response to Environmental Agents

1991 Authorization: Indefinite

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$59,783,000	$62,024,000	+$2,241,000

Purpose and Method of Operation

Understanding biological responses to environmental agents is one key to understanding the human health effects of exposure to environmental agents, and the cornerstone to identifying those exposures which pose a hazard and threat of disease, disorders and defects in humans. A first step in understanding biological responses is identifying and characterizing those biological, chemical and physical environmental agents that are hazardous to health. By understanding the relationship between environmental exposures and the subsequent development of disease or biological injury, human health may be better protected.

The research grant program of the Institute is the primary mechanism for supporting the university scientist-based, interdisciplinary search for links between exposures to environmental agents and human health effects.

Rationale for the Budget Request

The 1991 budget request for these activities is $62,024,000, an increase of $2,241,000 from the comparable 1990 level. The request would support 311 research project grants, 17 research career awards, 13 other research grants, and the MBRS program.

NIEHS research has provided much of the information available today on air pollutants. Investigators are examining how several air pollutants interact to cause more illness than exposure to a single pollutant does. How much interaction occurs, and the major ingredients in the lung-damaging exposures are issues being addressed, as is the question of the respective contributions of indoor and outdoor air pollutants to human exposures.

Increasing attention to the depletion of protective ozone in the stratosphere as a threat to vision (cataracts), skin (carcinoma and melanoma), and agricultural productivity has been accompanied by concern about increasing ozone at ground level as a hazard to human health, alone and in pollutant combinations. Investigators have some evidence that low levels of ozone

exposure in the newborn lung have a detrimental effect on airway membrane development, compromising maturation of the lung's defense system in immature and adult animals.

Long-term support for basic research on the effects of lead continues to expand our knowledge of the subtle and persistent effects of this ubiquitous pollutant. The mechanisms by which lead affects childhood neurological development, and what the effects of lead mean to the future health and well-being of the lead-exposed individual are among the emerging areas in this work. Developing better methods to eliminate lead in and around children's homes and developing improved treatments for those who are already heavily exposed are important applied facets of lead research. In addition, more accurate and sensitive methods for measuring persistent body burdens of lead are being developed, part of the effort to understand the lifetime consequences of lead exposure.

Research into the effects of mercury, another significant environmental threat to human health, has followed much the same path as lead. Low-level exposures have attracted attention because health effects at lower and lower body burdens of mercury have been identified. Mercury-contaminated food has been the main source of human exposure. In the United States, increased consumption of freshwater and saltwater fish and other marine products have increased potential exposure to the most toxic form of mercury, methylmercury.

Scientists shared some of the developing information on the human health effects of mercury in a 1989 NIEHS conference. Global atmospheric transport of mercury, documented relatively recently, reaches even isolated freshwater lakes that are sources of food fish taken by subsistence, sport, and commercial fishermen. The deposited mercury is methylated by microorganisms, accumulates in the aquatic food chain, and reaches its highest levels in the highest predators, which happen to be the fish most sought as human food. Already, some states (e.g., Michigan and Wisconsin) issue alerts advising pregnant women to limit their consumption of fish from lakes where mercury levels are elevated. The contributing role of acid precipitation to the mercury problem was discussed at the conference, with investigators noting that the concentration of methyl mercury in a lake goes up as the acidity of the lake increases.

The development and use of biomarkers is an expanding area in NIEHS research. Biomarkers may be a way to fill a gap in epidemiological studies evaluating the health impacts of environmental chemicals: the lack of adequate exposure history for individuals in exposed populations. Biomarkers of the reaction of environmental agents with an individual's DNA or blood proteins can provide evidence of exposure and identify the agent. Biomarkers have the potential for identifying hazardous exposures before adverse health effects appear. This information can then be used in establishing exposure limits that minimize the likelihood of significant health impacts.

NIEHS investigators are looking at biomarkers in terms of mechanisms because understanding mechanisms of action and of environmental exposure would enhance risk assessment and epidemiologic studies. For example, an improved

understanding of mechanisms will provide markers of biologically effective dose and carcinogenic response that are relevant in the early steps in the development of cancer, measured both in experimental systems and in humans. The public health significance of this information is its application to better measures to prevent cancer.

Using the tools of molecular biology, a biological system has been established whereby the genetic changes that occur for a single DNA adduct can be determined in bacteria or mammalian cells. This is the first site-specific experimental system of its kind, and these studies have the potential to provide important insights into early biological effects of environmental exposures.

National Institute of Environmental Health Sciences

Applied Toxicological Research and Testing

1991 Authorization: Indefinite

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$60,080,000	$61,041,000	+$961,000

Purpose and Method of Operation

Funds in this account support studies to characterize chemical toxicity and to improve the testing methods used to determine toxicity. Research grants and research and development contracts are used in accomplishing the applied toxicological research and testing mission within the Division of Toxicology Research and Testing.

The Division of Toxicology Research and Testing, one of four divisions within the National Institute of Environmental Health Sciences, is the core and largest component of the National Toxicology Program (NTP). The Division's resources are the Institute's contribution to the NTP, a cooperative intragovernmental program for testing chemicals with the potential for producing substantial human health effects.

Chemicals are nominated for testing by federal agencies, industry, and the public because of their potential for widespread human exposures and because of past experience with the test material or closely related substances. Chemicals are selected for testing based on their potential for human exposure and possible health effects and the testing program's available resources. The information developed may then be used by regulatory agencies and others to protect public health.

Rationale for the Budget Request

The 1991 budget request for this activity is $61,041,000, an increase of $961,000 over the 1990 comparable level. The request would fund 33 research project grants, 1 research career award, the MBRS program, and 172 research and development contracts.

The overall mission of the division is to expand the quality and scope of scientific information on the toxicologic properties of chemicals through developing, evaluating, and validating experimental procedures, and then sharing the information on health effects of the chemicals to protect public health and prevent chemically-induced diseases.

During FY 1989, more than 175 chemicals were in the toxicity and carcinogenicity testing process. Twenty-three draft NTP Technical Reports on toxicology and carcinogenesis were reviewed in public sessions of the NTP Board of Scientific Counselors.

There was some good news and some bad news from toxicity testing in the past year. In the good news was word that amphetamine, which is an important pharmaceutical, the riot control agent mace, and vinyl toluene, an important industrial chemical, do not cause cancer in experimental animals. However, when the Division completed its study on tetranitromethane, a rocket propellant compound and explosive mixture that showed unprecedented lung tumor-causing properties, the program had already alerted the Department of Defense and worker representatives to the potential hazard. Glycidol, an intermediate in the production of certain pharmaceuticals, was another clearly carcinogenic chemical in the testing program. Glycidol produced a number of different tumors in the tests.

In a new approach designed to incorporate the strengths of research at the Institute, in academia, and in industry, the Division began a project that will examine a number of different toxic effects of ozone in well-known animal models. Rats and mice are being exposed to ozone under carefully controlled conditions at levels experienced by some segments of the American public. The animals will be then be thoroughly studied for both systemic toxicity and cancer by scientists at the Institute and in other laboratories.

Because ozone inhalation exposures are so difficult to control and expensive to produce in individual laboratories, such a broad range of studies in so many laboratories would not otherwise be possible. In addition to a number of standard toxicological measures, the project will cover a longer period of exposure in order to ask whether older animals may respond differently to ozone exposures. The project includes a co-carcinogenesis study in which joint exposure to ozone and NNK, a well-characterized cancer-causing ingredient of tobacco smoke, will be used to see whether the effects of combined exposure may be synergistic.

In other projects within this category, the effects of environmental agents on fertility and reproduction are being explored in an assortment of efforts that use continuous breeding experiments, asking whether the number of offspring or their health and development are affected.

In work with far-reaching implications, the techniques of genetic engineering have enhanced by 10 to 1,000 times the sensitivity of human cell culture systems used to study how chemicals interact with cells, making it possible to look for mutagenic effects at much lower doses. In other efforts to improve carcinogenicity testing, the role of diet (quality and quantity) in explaining the old observation that underfed animals are less susceptible to carcinogens is being examined, and differences in the patterns of cancer-associated genes in spontaneous and chemically-induced tumors is being probed at the molecular level. NIEHS scientists are collaborating in developing transgenic mice which may improve sensitivity in the tests.

National Institute of Environmental Health Sciences

Biometry and Risk Assessment

1991 Authorization: Indefinite

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$9,783,000	$10,018,000	+$235,000

Purpose and Method of Operation

The Institute's activities in biometry and risk assessment include planning and conducting basic and applied research in quantitative and biochemical risk assessment, statistics, biomathematics, epidemiology, molecular modeling, and evaluation of basic concepts in toxicology.

An important focus of this research, which is centered in the Division of Biometry and Risk Assessment, is qualitative and quantitative estimates of the adverse health effects of exposure to hazardous environmental agents, and the development of experimental and computer modeling methods that are useful in this process. NIEHS scientists are seeking to identify environmental risk factors and the biological mechanisms that are involved.

Rationale for the Budget Request

The 1991 budget request for this activity is $10,018,000, an increase of $235,000 over the 1990 comparable level. The request would fund 16 research project grants, 4 research career awards, the MBRS program, and 10 research and development contracts.

The 24 Cities Study of air pollution and human health has begun, building on information developed in the classic Six Cities Study, the foundation for much of the current understanding of the health effects of indoor and outdoor air pollutants. A key finding of the Six Cities Study was that children, in general, are more susceptible to the adverse health effects of air pollutants than adults. The 24 Cities Study now focuses on the effects of acid aerosols on school-age children. By the time the study is completed, some 13,000 young people will have been examined and their pulmonary health evaluated against the air quality of their daily environment in 20 cities in the United States and four in Canada. Already, evidence is growing for a major role of acid aerosols, the mists and fogs made acidic by oxides of nitrogen and sulfur, in damaging normal lungs (bronchitis). In a separate study, investigators are looking at the link between levels of acid aerosols in ambient air and hospital admissions for respiratory problems.

Some investigations of the neurological damage associated with lead exposure also come under this category. Infants born with high blood lead levels have lower scores on the standardized test of learning and motor skills. With no additional exposure, these lead-affected babies begin to show some recovery or catch-up in neurobehavioral development by the age of two. On the other hand, infants and children exposed to lead during their first two years after birth, and with high blood lead levels, show adverse effects in mental development and hearing that persist at five years of age. A group of young people followed from grade school to the end of their teenage years showed increased incidence of reading disability and failure to graduate from high school for those with the highest body burdens of lead. The high lead burden group also showed a variety of motor problems, including poorer eye-hand coordination and longer reaction times. Other studies of more basic brain functions also suggest permanent neurological damage from lead exposure.

Contracts under this activity provide support to several major intramural projects. One of these supported projects is an epidemiological study of renal disease, an understudied but deadly illness, often leading to dialysis treatment or dangerous transplant surgery. NIEHS epidemiologists have reported a link between long-term, daily use of the over-the-counter painkiller acetaminophen and risk of kidney disease. Increased risk of kidney disease was observed among older men who use other non-steroidal analgesics. Also, exposures to organic solvents appear to increase the risk for a specific kind of kidney disease, glomerulonephritis. The continuing effort to learn which environmental factors or chemical exposures produce renal disease is important both clinically and for public health, since the illness is preventable and may be reversible if diagnosed early.

An epidemiological study of fetal death and pesticide exposure is supported in this activity. The study is comparing historical pesticide use in locations in the San Joaquin Valley of California with fetal deaths and live births to see whether a link exists between exposure to pesticide residues and fetal death.

Another contract supports a NIEHS project that is detecting oncogenes in cancerous tissue. NIEHS scientists are identifying the changes that have occurred to turn normal genes "on" and into a component of neoplasia. This is part of an effort to distinguish between "naturally occurring" tumors and those that are chemically caused. NIEHS scientists have also detected two new oncogenes in human lung tumors and are attempting to characterize these; and the scientists are pursuing promising new computer tools in molecular modeling of ras oncogene proteins.

The relevance to human health hazard of chemically induced, benign neoplasms in laboratory animals was evaluated using data from 143 long-term carcinogenesis studies. Only five or 3.5 percent of the tested chemicals induced benign neoplasia alone, and those observed benign neoplasms are known to progress to malignancy. Based on current knowledge of tumor progression and on the clear relationships between benign and malignant neoplasia, chemically induced benign neoplasia is an important toxicologic indicator of a chemical's carcinogenic potential in rodents and should continue as part of

the evidence evaluation process for identifying potential human health hazards.

In a project with major public health significance, the role of indoor exposure to radon or radon plus tobacco smoke in lung cancer is being explored. Investigators are gathering detailed data on exposures in an effort to distinguish among the components of increased cancer risk where radon daughter exposure is elevated.

National Institute of Environmental Health Sciences

Resource and Manpower Development

1991 Authorization: Indefinite

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$27,136,000	$27,136,000	---

Purpose and Method of Operation

The National Institute of Environmental Health Sciences supports the training of environmental health scientists and the development of focal national resources in environmental public health through three major grant programs: Environmental Health Sciences Core Centers, Marine and Freshwater Biomedical Sciences Centers, and research manpower development programs.

NIEHS is the major Federal agency with a program of support for training scientists for careers in basic and applied research into the human health implications of chemical and other environmental exposures. The Institute's National Research Service Awards support scientists who are being trained in toxicology, pathology, mutagenesis, epidemiology and biostatistics. There is an emerging need to train scientists in molecular epidemiology, to provide the bridge between classical toxicology and modern molecular biology. Other NIEHS programs support veterinary pathologists and physicians as they train for research in environmental and occupational epidemiology and medicine.

The NIEHS training programs include institutional training grants and postdoctoral fellowships; Mid-Career Development Awards; Physician Scientist Awards; and Clinical Investigator Awards. A new program of academic awards to address the need for emphasis on environmental/occupational medicine in medical school curriculums is planned for FY 91. All support the application of basic science skills to understanding environmental health issues.

Rationale for the Budget Request

The 1991 budget request for this activity is $27,136,000, the same amount as the 1990 comparable level. The number of centers being supported is 17, 12 Environmental Health Sciences Centers and five Marine and Freshwater Biological Sciences Centers for $16,550,000. A total of 459 research trainees would be supported for $10,586,000.

The Environmental Health Sciences Centers attract scientists from a number of fields in a setting that fosters collaboration, cooperation, and a coordinated approach to addressing the complex questions of environmental

public health. These center grants have flexibility that permits the centers to respond to new environmental health research needs locally, regionally, nationally, and internationally, in a timely manner.

Each of the centers has special areas of expertise-- metals; agricultural chemicals; occupational and industrial health; air, water, and food pollution. Around these areas, the center scientists ask far-reaching questions about how environmental agents affect human health, how the body responds, what the earliest indicators of exposure may be, and how populations respond to exposure. The Marine and Freshwater centers are employing aquatic species as biological models for studying chemically induced diseases and disorders, and as sentinel species to detect levels of pollution of concern for human health. The broad centers program is a national resource for research and manpower development in environmental health sciences.

Among the identified national manpower needs these centers address are training toxicologists and other environmental health scientists in using the new tools of molecular biology and risk assessment, and attracting more young United States citizens, including minorities and women, into the environmental health sciences.

National Institute of Environmental Health Sciences

Intramural Research

1991 Authorization: Indefinite

Budget Authority:

FY 1990 Appropriation		FY 1991 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA
586	$64,678,000	594	$67,840,000	+8	+$3,162,000

Purpose and Method of Operation

In concert with the primary mission of the National Institutes of Health, intramural research within the Institute is based on a continuing commitment to developing the science base required to address current and future public health issues, including the interactions between a changing environment and human health and well-being. Among the disciplines that cooperate and collaborate throughout the Institute are neuroscience, pharmacology, reproductive and developmental biology, chemistry, biophysics, genetics, carcinogenesis, and pulmonary pathobiology.

Such cooperation allows evolving research findings and procedures to be applied in a timely manner to toxicological issues that have not yielded to more traditional approaches. A number of intramural scientists are investigating the mechanisms underlying various human diseases, emphasizing those diseases which may have environmental components.

Rationale for the Budget Request

The 1991 budget request for Intramural Research is $67,840,000, an increase of $3,162,000 over the 1990 comparable level. This request would provide for built-in increases and modest program support increases.

Significant developments in FY 1989 included a deeper understanding of the way in which living cells go about the necessary work of reproducing their genetic code accurately, repairing spontaneous and induced damage to the code, and interpreting the signals of altered and unaltered genetic information. NIEHS scientists have identified chromosomes that appear to be responsible for suppressing a number of specific tumors, and other chromosomes that are altered when a precancerous cell escapes the normal growth control of cellular senescence or aging.

Lung diseases, cancer and developmentally-linked diseases are areas of intense study. Investigators have collaborated in generating an epithelial cell line from the airways of a cystic fibrosis patient, a cell line that

will improve scientists' ability to evaluate the molecular basis of the disease, with the potential for producing information useful in developing treatments.

Progress has been made on several fronts in identifying sensitive sites of mutagenesis in cellular DNA, such as very basic changes in genetic information that may affect structure and function of cells. Sensitive periods in cell growth for mutagenesis have been determined, and methods for detecting mutagenesis in mammalian germ cells have been developed. Scientists working with yeast and fruit flies are searching for mechanisms of mutagenesis, and are examining in vitro genetic toxicity assays plus in vivo cytogenetic effects for an improved predictor of tumor-causing chemicals.

In research related to asbestos-induced lung disease, fiber-induced changes in lung cell products that, in turn, stimulate lung fibrosis were ascertained and described. NIEHS scientists have identified a new oncogene that is activated in human mesothelioma, the rare, malignant tumor caused by asbestos exposure. The information is being used to seek a diagnostic marker for preclinical disease.

In the realm of developmentally-induced disease, investigators found responses to estrogen, a female hormone, very early in development in cells that were not known to have classical estrogen receptors. The research indicates that estrogen can misprogram hormone-induced genes in the male genital tract, suggesting how the proposed association between estrogen exposure early in life and the adult onset of prostatic cancer works.

By evaluating ovarian function as a target for toxic effects, and then doing tissue examination of the ovaries to look for structural changes associated with functional change, Institute scientists are developing and refining methods for assessing effects of chemicals on female reproductive capacity. Projects on male fertility and postnatal toxicity are examining the utility of the rabbit for studying effects of chemicals on semen, the rat as the model for transfer of chemicals through breast milk to offspring, and mice as the model for the effect of chemicals on the developing immune system.

In other work related to reproduction and fertility, investigators found that women exposed before birth to their mother's cigarette smoking were substantially less fertile as adults. These scientists also showed, in preliminary data, an association between exposure to nitrous oxide exposure and decreased fertility in dental technicians. In methods development, investigators have produced a new method for identifying day of ovulation, an important step in developing statistical models to help understand the effects of environmental agents on reproduction and fertility.

The kidneys are a key organ in the way environmental agents are handled in humans and other species. Research here has answered an important question in renal transport of foreign materials by explaining how the active transport process is coupled to cell metabolism. Two carrier proteins are involved, providing a basis to begin to study kidney membrane transport at the molecular and genetic levels.

As described in Biometry and Risk Assessment, investigators are evaluating environmental risk factors associated with kidney disease, in particular the association between long-term use of analgesics and kidney dysfunction.

Using some of the most exciting new techniques in molecular biology, NIEHS scientists have developed a model based on adrenal medulla cells to study gene regulation in the nervous system. This approach emphasizes long-term actions on gene expression and has led to new concepts in neurotransmission and neuromodulation which may provide more insights into the effects of psychoactive drugs.

And, in research into one of the most basic human systems for metabolizing and bioactivating foreign chemicals, the cytochrome P450 enzyme, NIEHS scientists have shown how a single amino acid substitution (one changed coding unit in the enzyme's genetic information) can completely change the substrate specificity of the enzyme, that is, the foreign chemical the cytochrome P450 recognizes and acts on.

National Institute of Environmental Health Sciences

Research Management and Support

1991 Authorization: Indefinite

Budget Authority:

FY 1990 Appropriation		FY 1991 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA
87	$7,279,000	89	$7,733,000	+2	+$454,000

Purpose and Method of Operation

Research management and support provides salary and other support for the immediate Office of the Institute Director, the Division of Extramural Research and Training, and portions of the Office of Management. Directing, coordinating and evaluating Institute-wide programs and policies and reviewing and administering grants, contracts and cooperative agreements are among the responsibilities covered by this activity. Central financial and personnel management, and the Institute's information office, are funded in this category.

Support for some functions of the National Toxicology Program (NTP) is included in this budget activity. The Institute Director is also the Director of the NTP and is responsible for coordinating the NTP-related programs of NIEHS and other federal agencies that take part in the government-wide program to identify environmental agents with the potential to affect human health.

Rationale for the Budget Request

The 1991 budget request for research management and support is $7,733,000, an increase of $454,000 from the 1990 comparable level.

Staff in the Division of Extramural Research and Training administer the Institute's responsibilities both in the traditional grant program and in the Superfund Program. The Superfund worker training program and the Superfund basic research program are the focus of intense review procedures to assure the best use of those resources. New approaches to tracking grants permit better monitoring and identification of special needs in the traditional program.

The Office of the Director continued efforts to respond in a timely manner to developing environmental health issues. Examples include the conference on the human health impacts of the Alaskan oil spill and the conference on the human health implications of global climate change. The Alaskan oil spill conference alerted the scientific community to how little information is available on the effects of crude oil in the environment on

in the environment, including seafood, from the spilled oil. The conference on potential human health implications of global warming was the first to address this topic, which is likely to be with us for a long time. Other meetings on continuing developments in studies of lead, mercury, fibers, and air pollution helped focus the attention of scientists and the broader public health community on lingering questions that must be answered to further the protection of human health.

The National Toxicology Program made progress in its studies of mixtures of chemicals that have been detected in agricultural, industrial, and waste sites. Reports of short-term tests on several chemicals found in Superfund sites have been speeded, permitting peer review of the studies sooner, and contributing to a timely evaluation of the information for regulatory agencies.

In the budget office, improved formats for reporting expenditures have made this budget information easier to use at the operating levels where many of the obligating decisions originate.

Architectural and engineering plans for additions to the permanent facility are complete, wrapping up most of the pre-construction phase of this project, which will eventually allow operations to leave temporary leased facilities.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Detail of Permanent Positions

	1989 Actual	1990 Appropriation	1991 Estimate
ES-4	9	9	9
ES-2	1	1	1
Subtotal	10	10	10
GS/GM-15	27	27	27
GS/GM-14	48	49	50
GS/GM-13	49	50	52
GS-12	31	32	33
GS-11	42	46	46
GS-10	2	2	2
GS-9	88	89	89
GS-8	4	4	4
GS-7	54	57	58
GS-6	45	48	48
GS-5	37	38	38
GS-4	15	15	15
GS-3	1	1	1
Subtotal	443	458	463
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	1	1	1
Director Grade	6	5	5
Senior Grade	3	3	3
Full Grade	3	3	3
Senior Assistant Grade	1	1	1
Subtotal	14	13	13
Ungraded	36	36	36
Total permanent positions	503	517	522

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

New Positions Requested

	1991		
Intramural Research	Grade	Number	Annual Salary
Epidemiologist	GS-14	1	$ 50,342
Chemical Manager	GS-13	1	42,601
Research Chemist	GS-13	1	42,601
Research Biologist	GS-12	1	35,825
Bio Lab Technician	GS- 7	1	20,195
		5	191,564

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Advisory and Assistance Services

For FY 1991, the Advisory and Assistance Services budget will be $242,000, an increase of $8,000 over 1990. The emergence of newly recognized environmental issues such as global warming, stratospheric ozone depletion, and hazards from emerging technologies has forced NIEHS to expand the kinds of research it conducts and supports. NIEHS is being asked to embark on such efforts as toxicological studies of compounds used to replace CFCs and to re-examine the relationship between non-ionizing radiation and soft-tissue cancers. This new research can be accomplished more quickly, more precisely, and more cost-effectively if the plans are subjected to careful outside evaluation and pilot tests. Expert consultation from scientists representing many disciplines will help anticipate and resolve highly complex new problems in the environmental health sciences.

The National Institute of Environmental Health Sciences (NIEHS) conducts a broad range of basic and applied biomedical research into the potential effects of exposures to environmental hazards on human health. It is critical that design and conduct of these studies and their findings be subjected to rigorous scientific peer review. These peer reviews must be conducted by individuals who possess extensive scientific knowledge and experience in fields as diverse as toxicology, clinical and gross pathology, epidemiology, biostatistics and biomathematics, and all of the sub-specialties of medicine. These individuals must be scientifically expert in their fields, yet at the same time they must be "entirely disinterested." That means that they cannot have or be perceived to have a financial or professional benefit which might accrue to them from the NIEHS study. For this reason, NIEHS staff scientists and scientist-managers, no matter how talented and accomplished they may be, must routinely rely on individual expert consultants to monitor their work and subject it to critical, public review.

At NIEHS the requirement for Advisory and Assistance Services arises almost entirely from the need for scientific peer review. The need is not only generated by the Institute's desire to assure that the research it conducts and supports is at the cutting edge of environmental sciences, but also is due to the tremendous potential for impacts on the U.S. economy and competitiveness in the world market. The results of these NIEHS studies are used by scientists, engineers, and program managers in regulatory agencies at the State, federal, and international levels. These officials often use data from NIEHS studies in preparing assessments of the risks to human health and ecologic systems posed by man-made or naturally-occurring hazardous substances. These "risk assessments" are used by economists, lawyers, policy makers and elected officials in regulatory and other actions to manage risk and to protect human health and environmental systems. Such regulations affect the lives of individuals, governments, and industry.

To ensure appropriate use of consulting services, the NIEHS has established a review procedure involving all appropriate administrative and management personnel. Proposals are reviewed by the pertinent Administrative Officers, the Committee Management Officer, the Budget Officer, the Executive Officer, appropriate program managers, and the Director as necessary. All NIEHS consultants are required to comply with applicable rules regarding conflict of interest. These rules are applied when a consultant is initially hired and re-emphasized at the time the consultant actually performs a specific service to the Institute.

THURSDAY, MARCH 15, 1990.

NATIONAL INSTITUTE ON AGING

WITNESSES

DR. T. FRANKLIN WILLIAMS, DIRECTOR
DR. WILLIAM F. RAUB, ACTING DIRECTOR, NIH
DR. GENE D. COHEN, DEPUTY DIRECTOR, NIA
DAVID L. CHICCHIRICHI, EXECUTIVE OFFICER, NIA
KARYN S. ROSS, BUDGET OFFICER, NIA
DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DHHS

Mr. NATCHER. At this time we take up the budget request for the fiscal year 1991 for the National Institute on Aging.

We have before the committee Dr. Williams, the Director of the Institute. And Doctor, before you give us your statement, tell us who you have with you there at the table.

Dr. WILLIAMS. Thank you very much, Congressman Natcher.

I have to the far left, David Chicchirichi, our Executive Officer; Dr. Gene Cohen, our Deputy Director; and Karyn Ross, our Budget Officer.

Mr. NATCHER. Thank you very much.

And now, Doctor, we would be pleased to hear from you.

HISTORIC TIME FOR AGING RESEARCH

Dr. WILLIAMS. Thank you, Mr. Chairman. This is very much a historic moment in time in the field of aging, not only because major advances in research are coming to fruition, but also because we now have three subspecialties in geriatrics in the fields of family practice, internal medicine, and psychiatry. This indicates the widespread recognition of this area of knowledge and its application to care.

ALZHEIMER'S DISEASE

I want to touch on a few highlights in our research areas of special emphasis and priority. Certainly the greatest emphasis of our Institute is on the health crisis produced by Alzheimer's disease in older people. Over 4 million people in this country have this disease, and it is now imperative that we halt this growing epidemic through more research. I have previously said that we must reach the goal of halting this disease within this century.

There are many lines of research that are quite promising, including advances in understanding the genetics that underlie some forms of this disease, the possible role of neurotoxic substances and infectious agents, and the possibility that Alzheimer's disease may be a widespread systemic disorder. For example, recent studies supported by our Institute show the amyloid changes characteristic of

this disease are found in the cells of skin as well as brain. This may, among other things, lead to a more simple and definitive diagnostic test which could save as much as $1 billion a year.

One of the most promising areas of research in my judgment is that on nerve growth factor which can influence the survival or regeneration of brain cells following injury. We hope within the next 2 years to begin clinical trials on nerve growth factor in Alzheimer's disease, and foresee its use in other degenerative diseases.

PHYSICAL FRAILTY

Another area of major importance is that of physical frailty and the role rehabilitative approaches play in restoring and maintaining independence in older people, which is the greatest goal of all of us and all older people. Research emphasis is placed on the roles that falls, hip fractures, and diseases such as osteoporosis play in frailty and on efforts to restore function as well as prevent these problems.

An overall related goal is that of health maintenance in older people and the key role of maintaining physical activity. Many studies now show the great benefits of maintained physical activity in sustaining health and independence of life in later years. We have a very active information dissemination program, through our Age Pages and other efforts, to help spread the interest and participation in healthful lifestyles.

CELLULAR SENESCENCE

A third area of exciting research is that of cellular senescence and the genetic basis for the decline in cell proliferation. This work is done primarily with human skin fibroblasts, cell cultures from the skins of humans, which show that in prolonged cultures or in cells removed from older people, there are genes brought into action which then depress further cell proliferation. There are also now proteins that can be isolated and put into young cell systems to depress cell proliferation. Just in the last few weeks there have been reports of findings which show that one of the major oncogenes, the C-fos gene, is turned off in the cell lines of these late proliferating senescent cell lines. Another very recent report shows that there are genes, one of which has been identified on human chromosome 1, which will also turn off an oncogene of this type. This provides a great opportunity to understand the aging process itself, plus the potential that some of these genetic findings have for opposing cancer.

SPECIAL POPULATIONS

We continue our strong commitment to research on special populations of older people, including those in rural settings and all minority groups, as well as worldwide comparative studies on populations and cultures. We are following up on the recommendations of our minority task force with new initiatives. This year we will fund two centers on Rural Health and Aging, and we plan to initiate a project on health and retirement as suggested by Congress.

RESEARCH TRAINING

We also continue to give priority to training for research and academic leadership in aging and geriatrics, including our Pepper Geriatric Research and Training Centers. Just to indicate the widespread interest in the major areas of our research, I would like to give you these recent issues of *Newsweek,* in which the cover stories dealt with Alzheimer's disease and with the whole topic of aging and maintenance of good health.

Our FY 1991 budget request is $248,938,000. I would be very happy to answer questions.

[The prepared statement of the Director, National Institute on Aging follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Institute on Aging

The field of aging has increasingly attracted major scientific interest since 1974, when the National Institute on Aging was established. Over the past 15 years, there has been an unprecedented and exponential growth of new and exciting research opportunities. It is important to recognize that we are very much at a historic moment for the field of aging--a period marked by advances in new frontier research. A reflection of this historic development has been the establishment of three new subspecialties in geriatrics. Fifteen years ago it was difficult to find even a handful of medical schools in the country with a special focus on older adults. Today, the fields of internal medicine, family practice, and psychiatry are each establishing a subspecialty in geriatrics--reflecting a whole new level of scientific curiosity and capacity to conduct research on aging. This is further reflected by the significant growth of high quality research grants approved for funding.

The conquest of Alzheimer's disease (AD) remains the NIA's most important priority. Other continuing priorities include understanding of the basic mechanisms and characteristics of aging; promotion of health, effective functioning, and quality of life--including prevention or reduction of physical frailty; long-term care and caregiving; special populations including the oldest old, older persons in rural settings, and minorities; and training and career development in aging research and geriatrics.

Alzheimer's disease has brought on a health crisis of epidemic proportions. It is one of the most prevalent, devastating, and costly diseases of later life. Recently published data indicate that AD may be more prevalent than previously reported. It is now estimated that 4 million people have AD at an estimated cost of $80 billion a year. It is imperative that we halt this growing epidemic through further research.

While progress is being made in understanding AD, we do not yet know the cause(s). Studies on the genetics of AD have shown that there is a linkage between chromosome 21 and the early onset familial form of AD. Recently, studies have begun to yield results that establish an association between chromosome 19 and late onset AD. Other leads on the possible cause of AD suggest that aging may increase susceptibility of the nervous system to toxins and other environmental perturbations. There is growing evidence that neurotoxins cause specific nerve cells to die, thus contributing to the etiology of AD.

Preliminary evidence has indicated that AD may be caused by an infectious agent. Confirmation of these results through additional research is an urgent need. Such research is critical before we can be sure whether some cases of AD have an infectious

origin. A multi-center replicative trial is currently under consideration to test this hypothesis.

An abnormal protein, amyloid beta-protein, which is associated with the hallmark of AD brain pathology, has now been found in non-neuronal tissues such as the skin, subcutaneous tissue, and intestine. These data suggest that AD could possibly be a widespread systemic disorder, and support other findings indicative of a metabolic defect in AD. Research in this area suggests that abnormal processing of the amyloid precursor protein could be a consequence of this disease and produce some of the cellular events associated with AD.

Researchers are now finding ways to slow down or prevent cell loss by stimulating the brain with chemicals used to promote cell growth during development. Since AD involves massive cell death, such work has important implications for developing treatments. More specifically, it has been shown that nerve growth factor (NGF) can be administered to targeted areas of the brain in experimental animals such as mice and will produce nerve growth and improve function. A goal is to determine the potential use of NGF and similar substances to prevent or correct cell loss in Alzheimer's and other degenerative diseases.

In relation to the possibility of treating and minimizing the effects of AD through use of medications, the clinical trial on the efficacy and safety of tetrahydroaminoacridine (THA) is proceeding as planned, with the expectation of definitive answers within this fiscal year. There are, moreover, additional AD drugs emerging as candidates for clinical trials.

Understanding the basic mechanisms of aging is an important step in the process of identifying interventions to delay or modify human aging. NIA is introducing a research initiative to determine the mechanisms by which lower consumption of calories dramatically lengthens life span and prevents age-related diseases, such as cancer, in experimental animals. Learning these mechanisms can reveal how these age-associated changes could be prevented or delayed in humans. Researchers supported by NIA are studying age-related changes in cell proliferation--why certain cells in laboratory chemical cultures have a limited life span. The results of one such study just reported this January uncovered new clues about the molecular basis of cellular senescence. A repressed gene was identified, along with a reduced amount of a protein considered essential for normal cell division. Such results have potentially major ramifications not only for understanding underlying mechanisms of aging but in providing new ideas about cancer intervention as well. Whereas in aging, cell proliferation slows, in cancer it grows out of control; cellular mechanims regulating aging may potentially be influenced to regulate various cancers.

A major goal of the NIA is to help older people maintain an independent life style and to reduce the risk of needing long-term care. Physical frailty significantly diminishes the ability to conduct common activities of daily living, and increases risk of falls and hip fractures. Preventive and rehabilitative strategies, however, show strong promise for reducing frailty and injuries.

For example, a large scale study has shown that a comprehensive falls prevention program can significantly reduce the number of falls in older people. Other studies have shown that older persons who fall have weaker leg muscles than others of the same age who don't fall, while related studies show that exercise can dramatically restore leg strength even in very old frail 90-year-old nursing home residents. In 1990, NIA and the National Center for Nursing Research will jointly initiate the Frailty Clinical Trials, to test interventions to reduce physical frailty and its consequences in older persons.

Another aspect of the frailty initiative is NIA's osteoporosis program which has a special focus on aging-associated aspects of this disease. Because bone loss is almost universal with increasing age, NIA supports research to identify age-associated processes responsible for osteoporosis, and to develop prevention and treatment strategies based on modifying them. Such strategies offer the promise of fundamental major progress in preventing or curing this disease. NIA especially emphasizes osteoporosis in advanced age, when it is most severe and causes the most severe disability and mortality, especially from hip fractures. Because many aging processes are modifiable by exercise, nutrition, and other factors, NIA is placing increasing emphasis on testing interventions against osteoporosis. Interventions developed through NIA's frailty and osteoporosis initiatives could result in major reductions in future long-term care needs.

Geriatric rehabilitation is an area of increasing NIA emphasis. In May 1989, NIA issued a program announcement encouraging research on biomedical and psychosocial aspects of rehabilitation for older persons. In 1990, the NIA will solicit applications for Special Emphasis Research Career Awards in Rehabilitation and Aging. These awards will provide five years of career development support aimed at increasing the small number of researchers with expertise in both aging and rehabilitation. Rehabilitation looked at within the context of aging will also add significantly to reducing the burdens of long-term care.

NIA intramural researchers and researchers supported in other settings are studying the extent to which exercise regimens can forestall or ease age-associated physiological decrements, inhibit the development of diseases, and increase longevity. Accumulating evidence suggests that expected age-associated changes in such physiologic parameters as blood glucose tolerance, skeletal muscle strength, and cardiac measures occur to a lesser extent--if at all--in physically fit older persons. Increased research attention is needed on the problem of cardiovascular disease in older persons. Despite progress in preventing cardiovascular disease in middle age, important questions remain about the effectiveness of current prevention strategies for older persons. Evidence indicates that new strategies, based on increased understanding of the relationship of aging to vascular disease, will be needed for optimal prevention of this major cause of death and disability among older persons. For example, recent studies have shown the high value of stress tolerance tests, using electrocardiograms and thallium scanning in predicting the

likelihood of a coronary event in the next 4-5 years--essentially the same high confidence in not having a coronary event in men aged 60-69 as in those age 40-59, if the stress test is normal.

The NIA has a strong commitment to research on the health and well-being of special aging populations such as the oldest old, older persons in rural settings, and minority groups in the United States, and older populations in cross-national and cross-cultural settings throughout the world. The NIA is studying the differences of life expectancy between blacks and whites, including behavioral and life-style antecedents. Ongoing epidemiological studies are examining variations in different ethnic and cultural groups in such topics as dementia, skin cancer, bone density, hypertension and diet, diabetes, sickle cell trait, and vision and hearing. Other studies are addressing intellectual functioning and family structure.

Older rural residents face many problems which affect them specifically because they live in rural areas. Problems of access to and affordability of medical and social services are particularly important for these individuals. Rural areas generally support a narrow range of services, have a higher proportion of poor and medically uninsured individuals than do urban areas, and face a continuing problem in recruiting and retaining health care professionals. Rural residents typically live at some distance from physicians, hospitals, and other social services, and do not have access to public transportation. The NIA has initiated a program of center grants on the health and well-being of older rural populations, and expects to fund two such centers in FY 1990.

The health care needs of a growing population of older persons will require increased numbers of geriatricians and other health care providers with training in geriatrics. These growing needs require more individuals capable of conducting research in geriatrics and training future geriatricians. In response to this need, the NIA has established the Claude D. Pepper Geriatric Research and Training Centers program. These centers are designed to enhance collaborative efforts in geriatric research and provide training and career development for academic geriatricians who will increase academic leadership in the field nationwide. Two centers have been funded.

NIA has a strong and growing interest in geriatric pharmacology. Older people commonly take several medications, which frequently interact to produce adverse effects. Yet too little is known about drug metabolism, pharmacodynamics, appropriate dosages of medicine needed by older people, or the causes of adverse drug reactions in older people and how to prevent them. Relatively few drugs have been thoroughly evaluated in older persons. Considerable difference in a drug's half-life can be observed in comparisons between young adults and older persons, indicating the potential need for very different prescribing patterns for older persons. The NIA plans a broad spectrum of basic and clinical research on the use and effectiveness of medications in older people.

Older people are, unfortunately, sometimes viewed as an unproductive drain on society; in reality they are an untapped national resource. Though older people may spend two to three decades of their lives in retirement, many want and are capable of continuing some form of productive activity. Extending productivity into the later years has obvious ramifications for national policy, yet little is known about how current work and retirement trends affect the physical and psychosocial functioning of aging individuals, or the degree to which they result in losses of productivity for society and older people themselves. Current NIA research on these issues will be supplemented by initiation of the longitudinal Health and Retirement Survey planned for 1990.

Mr. Chairman, the 1991 budget request for this Institute is $248,938,000. I will be happy to answer any questions.

BIOGRAPHICAL SKETCH
T. Franklin Williams, M.D.
Director, National Institute on Aging

Birthdate: November 26, 1921 - Belmont, North Carolina

Education: B.S., University of North Carolina, 1942; M.A., Columbia University, 1943; M.D., (Cum Laude) Harvard Medical School, 1950

Professional History: 1983 to present, Director, National Institute on Aging, NIH, 1983, J.Lowell Orbison Alumni Distinguished Service Professor; 1982-1983, Director of the Geriatric Unit, Monroe Community Hospital, Rochester, N.Y.; 1980-1983, Co-Director, Center on Aging, University of Rochester Medical Center; 1968-present, Professor of Medicine and of Preventive, Family and Rehabilitation Medicine, University of Rochester; 1968-1982, Medical Director, Monroe Community Hospital, Rochester, N.Y.; 1977, L.S. Mcleod Visiting Professor of Geriatric Medicine, University of Adelaide and South Australia Postgraduate Medical Education Association; 1956-1968, Instructor to Professor of Medicine and of Preventive Medicine, University of North Carolina; 1954-1956, Fellow in Medicine, University of North Carolina; 1953-1954, Assistant in Medicine, Boston University; 1953-1954, Senior Resident Physician, Boston Veterans Administration Hospital; 1950-1953, Intern and Assistant Resident Physician, John Hopkins Hospital; 1942-1943, Assistant in Chemistry, Columbia University.

Military Service: 1983 to present, Assistant Surgeon General, U.S. Public Health Service; 1943-1946, Communication Officer, U.S. Naval Reserve, active duty.

Societies and Associations: American Association for the Advancement of Science (Fellow); American College of Physicians (Fellow); American Federation for Clinical Research; American Public Health Association (Fellow); American Society of Human Genetics; American Geriatrics Society; American Diabetes Association; Society for Experimental Biology and Medicine Rochester Academy of Medicine; New York and Monroe County Medical Societies; Gerontological Society of America; New York State Public Health Association; Association of American Physicians; Institute of Medicine, National Academy of Sciences; The Royal Society of Medicine; and Academia Medicorum Litteratorum.

Honors and Awards: Phi Beta Kappa; Alpha Omega; Sigma Xi; Member, Institute of Medicine; Diplomate, American Board of Internal Medicine; Diplomate, National Board of Medical Examiners; Markle Scholar in the Medical Sciences; Special Fellow, Department of Physiocoloy, Vanderbilt University; Honorary Member, American Academy of Orthopedic Surgeons; and Honorary Doctor of Science, Medical College of Ohio.

Publications: Author of over 131 publications in journals and books.

NUMBER OF OLDER AMERICANS

Mr. NATCHER. Thank you, Dr. Williams.

Now, Doctor, if you will, just review for the committee briefly the basic facts on the changes taking place in the number of older Americans at various age levels.

If you would now just review that for us, please.

Dr. WILLIAMS. There is a continuing rise in the numbers of older people in our country. The numbers that are most impressive are those in the group age 85 and older which will increase from over 2,500,000 to over 5,000,000 by the year 2000. The population of people aged 65 and older will reach 20 percent of our total population by the year 2020, which is well within the lifetime of all of us here.

INCIDENCE OF ALZHEIMER'S DISEASE

Mr. NATCHER. Your statement mentioned, as you know, a new study in Boston which indicates that a much larger number of Americans may be vulnerable to Alzheimer's disease. What level of confidence do you have in this new research, Dr. Williams?

Dr. WILLIAMS. This research, published by Dr. Evans and colleagues in Boston, is based on a complete community study of all people over the age of 65 in East Boston. This is a well-defined population, in which a very careful evaluation was done to detect any evidence of cognitive or memory impairment.Those who were found to have some impairment were given careful clinical tests to determine if they clearly had Alzheimer's disease. The figures showed that in this population, a much higher proportion than we have seen in previous studies appeared to have the Alzheimer's disease clinical condition. In those over the age of 85, almost 50 percent were diagnosed as having Alzheimer's disease. When extrapolated to the country as a whole, this represents at least 4,000,000 Americans who have this disease.

The study was very carefully done, and is the only study we have thus far that has looked at all people in a defined population. We do have some reservations, however, concerning the projections to the Nation, and believe that the study does need to be replicated in other settings. We are encouraging that type of effort to determine to what extent this is exactly representative of the country.

The strongest point favoring the Boston study is the fact that it was a very careful examination of all older people. It is also an area where an unusually small proportion of people actually go into nursing homes. They have a well-developed home care program where families keep people at home to a higher degree than in other parts of the country. It is likely that other community surveys didn't take into full consideration people who may have moved into nursing homes.

While we have to take the Boston study seriously, it should be replicated.

INCREASED FUNDING

Mr. NATCHER. As you know, Dr. Williams, last year Congress added $9,000,000 to the President's budget request for your Institute. Other than identifying Alzheimer's disease as a priority, the

decision about how best to use this money was left largely to the Institute by the House.

If you will now tell us, how did you decide to use the increased amount, Doctor?

Dr. WILLIAMS. In making the decision, we took full recognition of both the House and Senate and the combined conference report recommendations. They were consistent in their advice to us which included, in addition to Alzheimer's disease, recommendations that we continue developing our support for rural health and aging.

In response to this we will fund two developmental centers for research on rural health and aging. In addition to the Alzheimer's disease field, we have strengthened support for research on frailty problems. Another area of emphasis, which was mentioned in both languages, is that of the Clause Pepper Geriatric Research and Training Centers.

Both House and Senate reports also recommended that we bring our staffing back up to 1983 levels. We will also extend our Alzheimer's disease outreach efforts by funding core centers and satellite clinical centers which will extend our ability to reach inner city, minority areas as well as rural populations. And finally, funds were provided for the Alzheimer's Disease Educational and Referral Center which will enhance our outreach efforts.

RESEARCH CENTERS

Mr. NATCHER. Your goal then, Dr. Williams, is to increase the number of centers from 18 to 24; is that correct?

Dr. WILLIAMS. Yes, sir, this year. We will add rural health and aging centers and another Claude Pepper Geriatric Research and Training Center. And as I just mentioned, we will fund core centers and satellite clinical centers in conjunction with the Alzheimer's Disease Research Centers.

Mr. NATCHER. In addition to the new centers in 1990, you also opened five new centers in 1989 for a total of 11 new centers, I believe, in two years, Dr. Williams.

The 1991 budget proposes downward negations of these centers' grants of about 27 percent. Wouldn't it be much better, Dr. Williams, to plan for more adequate levels of support for a smaller number of centers, rather than cuts of 27 percent per center?

Dr. WILLIAMS. This has been a very difficult issue for us, Mr. Chairman. We have examined the full range of the challenge of Alzheimer's disease to determine how best to serve the population with the few centers we have.

While the centers that we fund are very important, there are other sites throughout the country that have a great deal to offer in a leadership role as core centers for Alzheimer's disease. We are also adding satellite clinical centers to the existing Alzheimer's Disease Research Centers which will reach out to underserved areas, that is inner city, rural, and minority groups, to bring closer contact with a wider range of people who are at risk for Alzheimer's disease. These new types of centers will also expand our patient base for clinical trials which is critical for finding an appropriate treatment.

RESEARCH PROJECT GRANTS

Mr. NATCHER. Doctor, if you will, also explain to us about the increase in the number of research project grants and downward negation of the grants?

Dr. WILLIAMS. We will be negotiating downward our grants in the range of 10 to 15 percent.

Mr. NATCHER. Dr. Williams, as I understand now, you have decided not to use any part of the $9,000,000 increase for project grants?

Dr. WILLIAMS. We did increase research project grants by approximately $3.5 million. However, this amount was later reduced by sequestration and other mandatory reductions.

Mr. NATCHER. What was your original funding request for growth—$139,000,000?

Dr. WILLIAMS. Yes, sir. The original FY 1990 President's Budget requested $139,123,000 for research project grants. The FY 1990 appropriation provided $142,786,000 which was reduced by sequestration and other mandatory reductions to $139,697,000.

Mr. NATCHER. Take a look, Dr. Williams, when you get the transcript back now and check that little matter for us here and you can put in the amount.

Dr. WILLIAMS. Yes, sir.

[The information follows:]

HISTORY OF FY 1990 BUDGET

In making our decision to allocate funds by mechanism, the NIA very carefully analyzed the report language of both the House and Senate Appropriations Committees. The research areas highlighted by both houses of Congress also reflected NIA's own priorities. We thus provided increases to research project grants, research centers, research training, R&D contracts, intramural research and research management and support. These increases provided funding for Alzheimer's disease research, special populations such as the oldest old, minorities and rural elderly, research training, training supported through the Claude Pepper Geriatric Research and Training Centers which also have an Alzheimer's component, the Alzheimer's Disease Education and Referral Center, and restoring NIA's FTE level to that supported in FY 1983.

After these decisions were made, NIA was instructed to make reductions in its budget, as were all NIH institutes, centers and divisions, according to Congressional language. These reductions were for capping the principal investigators salary on grants and contracts at $120,000, procurement reductions, an extramural construction tap, and a salaries and expense reduction. Such reductions were taken in the appropriate mechanism. In addition, sequestration also called for further reductions which were mandated to be taken across the board on all mechanisms and on all programs, projects, and activities (PPAs) that were specifically identified in report language. The exact definition of the PPAs was determined by the Department of Health and Human Services, and for this, the Senate language was used since it had more specific earmarkings. The result of this was to reduce research project grants from $142,786,000 in the FY 1990 appropriation to $139,697,000 in the revised FY 1990.

In making its decisions on how to best take the cuts and to minimize reducing the number of competing research project grants (RPGs), NIH made the decision to increase the downard negotiations so that the number of competing RPGs could remain essentially the same as planned in the FY 1990 appropriation. For the National Institute on Aging, that meant keeping the number of competing RPGs at 156 while increasing the downward negotiations from the planned 12 percent for noncompeting awards to 13 percent and the planned 10 percent for competing awards to 15.5 percent.

In addition, since NIA gives importance to RPGs, we made the difficult decision to reduce our Centers awards by approximately 18 percent across the board in FY 1990 so that we would not have to reduce our research project grants any further. The centers also provide us with an important mechanism for generating new research

project grants, and thus it is vital that we maintain the number of center awards. It should also be noted that NIA's centers program is still quite new and has been largely Congressionally mandated. In making our decisions regarding downward negotiations, it was felt that we could not discontinue any of the ongoing centers, and that we must initiate the planned new centers. These new centers will provide us with Alzheimer's disease core centers and satellite clinical centers that will reach out to inner city, minority and rural areas. Besides reaching underserved areas, this will also allow us to increase the patient base from which to draw for testing potential new treatments for Alzheimer's disease. The Claude Pepper Geriatric Research and Training Centers and the Rural Health and Aging Centers, also mandated by Congress, also have an Alzheimer's component besides serving such purposes as increasing the number of new investigators and trainees in the field of geriatrics and reaching under served rural areas. Centers also provide an important tool in a new field to influence the intensity, growth and attract the best people to pursue research.

AVERAGE SIZE OF PROJECT GRANTS

Mr. NATCHER. After adjusting for downward negations, how will the average size of your 1990 project grants compare to 1989?

Dr. WILLIAMS. The total average cost in 1990 will be $264,792,000; in 1989 it is $230,600,000.

Mr. NATCHER. Mr. Conte, I yield to you.

CAUSE OF ALZHEIMER'S DISEASE

Mr. CONTE. Thank you, Mr. Chairman.

Dr. Williams, it is wonderful to see you again and have you before the committee. You are a forefront researcher in geriatric health, and through your efforts, our senior citizens are now benefiting from the fruits of your research many times over.

Of course, a lot more needs to be done, that is for sure, and you are laying the foundation for future breakthroughs in Alzheimer's, osteoporosis, and many other diseases.

Chairman Natcher and I, along with the rest of this committee, will work hard to see to it that you get the resources you need to do the best job you can.

Dr. WILLIAMS. Thank you, sir.

Mr. CONTE. The cost of Alzheimer's is simply staggering; $80,000,000,000 a year. But even more tragic than the cost is the toll of personal and family suffering caused by this disease.

Finding a way to prevent and halt the progression of Alzheimer's deserves our top priority in research.

You mentioned in your written statement about evidence that an infectious agent might be a potential cause of Alzheimer's. Any clue as to what that agent might be?

Dr. WILLIAMS. The research that this is based on was done at Yale University about a year and a half ago. Their findings showed that they could take white blood cells from members of families where there was a strong genetic predisposition for Alzheimer's disease, and inject these cells into the brains of hamsters. In about a year, half of these hamsters developed degenerative lesions in their brains. They then took material from the hamsters and injected it into another group of hamsters who also developed these lesions. The researchers had clear cut evidence for a transmissible or infectious agent, which was harbored, if you will, in the white cells of the susceptible people.

This is pretty solid evidence of the existence of a transmissible agent. One of the concerns has been that this could have resulted from a contaminate or other technical problem. We are funding two other sites to determine whether this research can be replicated.

If it is confirmed, it is possible that this transmissable agent may be almost any of a series of viruses that some people are especially susceptible to. It may be a virus that is common in all of us and harbored for a long time, eventually causing these changes.

Mr. CONTE. You got two projects going?

Dr. WILLIAMS. We are funding two entirely separate sites to test this hypothesis.

ROLE OF ALUMINUM

Mr. CONTE. Alzheimer's involves massive brain cell death. Are you working with the Neurology Institute to see if drugs that block the chemical process of cell death might help, and is there any definite word on whether aluminum plays any role in Alzheimer's?

We hear a lot about that.

Dr. WILLIAMS. That is quite a controversial subject and has been for some time. We are supporting several different research projects to determine whether aluminum is, in fact, an active agent in causing the type of damage seen in Alzheimer's disease. There is some evidence to strongly suggest it isn't.

We are also supporting studies which are examining positive environmental factors such as sprays used in agriculture that might possibly play a role. We are looking at the effects of neurotoxic brain transmitters which may, under certain circumstances, cause damage or cell death.

The glutamate transmitter, for example, is being looked at carefully. This is similar to work being done by the National Institute of Neurological Diseases and Stroke.

There is also potential for food chain toxins to cause Alzheimer's disease. Very provocative work from the island of Guam has identified a neurotoxic amino acid in one of their food substances that has probably caused degenerative brain damage in people in Guam.

DIAGNOSTIC IMAGING

Mr. CONTE. Are there any new advances in diagnostic imaging which may help with early detection of Alzheimer's disease?

Dr. WILLIAMS. There are several important findings. The most clear cut finding is the usefulness, when it is needed, of a second computer tommography scan, or CT scan, after the first CT scan, What has been clearly found in people who have Alzheimer's disease is that the brain substance, as shown up on CT scan, shrinks rapidly. A second CT scan as soon as even six months after the first one can show measurably less brain mass. That does not happen in normal people. Just this rate of change is a pretty strong diagnostic measure of Alzheimer's disease.

Magnetic resonance imaging is also being used to detect the vascular dementias, the small strokes or the multi-infarct type dementia, and certain other variants and to help make a differential diagnosis for Alzheimer's disease.

FRAILTY CLINICAL TRIALS

Mr. CONTE. Doctor, you along with the nursing research center will be starting the frailty clinical trials this year, and these studies will see whether certain strategies can be used to reduce disability and certain chronic disease.

What would be some of the long-term benefits of these trials, and are all the promising interventions being tested?

Dr. WILLIAMS. This is another very high priority area. It is the physical frailties as well as the mental frailties of the Alzheimer's type that are the greatest burdens of care and lead to the highest use of nursing homes. This clinical trial, funded in conjunction with the National Center for Nursing Research, will examine a variety of risks for frailty, problems of falls, hip fractures, arthritis and stroke. Frailty may also result from the lack of regular exercise which can be reversed through appropriate rehabilitative strategies.

NIA's frailty initiative can also be related to the recommendations of the Pepper Commission which very strongly recommended a major research agenda on factors of physical and mental frailty.

Mr. CONTE. Doctor, in your professional judgment, how much additional funds would be needed to reach an appropriate level for these studies?

Dr. WILLIAMS. In my professional judgment, Mr. Conte, we would need $25,000,000 to fully fund the opportunities available in the frailty initiative.

CLAUDE PEPPER CENTERS

Mr. CONTE. As the American population gets older and the baby boomers go bust, there will be a critical need for more health workers trained in geriatrics.

In your testimony, you said that the NIA began the Claude Pepper geriatric research and training centers program to develop the faculty needed to train future specialists.

How many Claude Pepper centers do we have, and have you funded, and in your professional judgment, how many of these centers are needed and how much funding is required to support them?

Dr. WILLIAMS. We have funded two Claude Pepper Geriatric Research and Training Centers. In our judgment, we could very well fund five more right now, which would require $6,000,000.

We anticipate in the long run, as recommended by the Institute of Medicine of the National Academy of Sciences, that there are 15 to 20 well qualified sites around the country for these centers. Our immediate goal, however, would be to fund at least five additional centers with already peer reviewed and approved applications of high priority.

Mr. CONTE. What constitutes a well-sited center?

Dr. WILLIAMS. This is a site where there is already a solid array of geriatric-related research. This would require several good investigators who are pursuing research in this area who are prepared and able to add new faculty members and trainees. This creates an environment for moving from the fellowship training level to full investigator status. This in turn would generate a larger number of

investigators who could provide further research and training opportunities.

Mr. CONTE. Thank you, Mr. Chairman.

Mr. NATCHER. Mr. Stokes, I yield to you.

Mr. STOKES. Thank you very much, Mr. Chairman.

Doctor, it's nice to see you again.

Dr. WILLIAMS. Yes, sir.

PEPPER COMMISSION

Mr. STOKES. You just mentioned, in reply to a question by Mr. Conte, the Pepper Commission.

Dr. WILLIAMS. Yes, sir.

Mr. STOKES. I served on that commission, and one of the recommendations in our report included a proposed funding level of $1,000,000,000 annually to support a research and development program aimed at preventing, delaying, and dealing with long-term illnesses and disabilities such as Alzheimer's and physical frailty.

I have two questions, Doctor. What is your reaction to that proposal, and then, secondly, in your professional judgment, is this level of funding a reasonable goal?

Dr. WILLIAMS. First of all, my reaction, Mr. Stokes. The recommendation from the Pepper Commission for a $1 billion funding level is extremely sound. As I have said before the only answer to the crisis we already have in long-term care needs, and the crisis that is going to occur with our growing population of older people, is through research.

We simply must halt these epidemics of Alzheimer's disease, which is costing $88,000,000,000 or more per year, hip fracture, which is costing $7,000,000,000 to $10,000,000,000 per year, and urinary incontinence and the other frailties, which cost over $10,000,000,000 per year, that can lead to long-term care, and create a burden both for care givers at home and in institutions like nursing homes and hospitals. This recommendation of the Pepper Commission is just fundamental. We must get control of this threat of long-term care.

In terms of the dollars, in my professional judgment, a goal of reaching $1,000,000,000 invested in this field within two or three years would be a very wise and achievable goal. There is no question that we can use such funding for existing and prospective research to solve the problem of long-term care.

Mr. STOKES. Thank you.

LIFE EXPECTANCY

Now, Doctor, in your formal statement, you tell us that NIH is studying the differences in life expectancy between blacks and whites. That is an area in which, if I understand it correctly, over the last few years, blacks have begun to lose ground.

What is the current data regarding this disparity, and what is being done regarding it?

Dr. WILLIAMS. You are correct, Mr. Stokes, that there has been a slight decline in black life expectancy, especially of black males as shown in the most recent data, compared to just two or three years ago. Between 1984 to 1987, the life expectancy in black males has

declined from about 65.6 to about 65.2 years, whereas in white males, it is about 72.2 years, and has been very slowly rising. For females, it is now about 78.9 for white females and it is around 73.6 in black females. Between 1984 to 1986 life expectancy declined about 0.2 years for black females, while there was a slight increase of 0.1 years between 1986 and 1987.

I believe I am correct that the female figure hasn't changed much, but it hasn't been rising for black females the way it has continued to rise slowly for white females.

Personally, I am looking forward to the 1990 census with a great deal of anticipation, because I think we will get more definitive data with a new census than currently available data.

Our institute is very much concerned with the factors that may be related to racial, ethnic, and cultural differences in survival, health, and all conditions that effect older people. We are approaching this in a number of ways.

We have constituted an advisory task force of leading scientists on minority health to meet with the National Advisory Council on Aging. They have provided recommendations for strengthening our research and training efforts in relation to minority issues and aging.

We already have some of these recommendations in place, such as a setaside of funds specifically for research on frailty problems in minority groups. We are also participating in the overall NIH program to support minority investigators through existing approved and funded research project grants to bring more investigators into the field. We are doing the same through our training program.

OLDEST OLD

Mr. STOKES. Doctor, in your statement you make reference a couple of times to the "oldest old".

Dr. WILLIAMS. Yes, sir.

Mr. STOKES. Who are we talking about when we refer to the "oldest old", and what type of special problems come with being in that category?

Dr. WILLIAMS. This represents an age range of people who are 85 and older. In the past, they have largely been left out of the statistics on older people, being counted with everybody aged 65 and older, as one group, the elderly. This is very misleading due to extreme individual variation as people get older and older. As I have already mentioned, the population age 85 and older will double between now and the year 2000, from about 2,500,000 to 5,000,000. This number will keep going up, and it is therefore vital that we learn more about their special needs.

And clearly, one of the biggest challenges is Alzheimer's disease. In the recently reported Boston study, 47 percent of the people over the age of 85 were significantly mentally impaired and probably have Alzheimer's disease. This is really a startling figure. About one in three white women over the age of 85 have hip fractures, another really disturbing figure. It is somewhat lower in black women, but still quite significant in men as well.

While we know something about this age group, one of our goals is to learn what constitutes effective, active continuation of independent living, and what part of those very late years are likely to be dependent or requiring long-term care.

INTERNATIONAL STUDIES

Mr. STOKES. Now, Doctor, I understand that NIA has explored opportunities for, and is developing plans to implement a variety of international and cross-cultural epidemiologic studies of dementia and other aging-related concerns.

What is the status of NIA's international activities and the activities of the World Health Organization's special programs on research on aging?

Dr. WILLIAMS. These international activities provide important opportunities to learn more about aging, for our own Nation's benefit as well as the rest of the world. We provide the home base for the World Health Organization's Special Program on Research in Aging at the request of the World Health Organization.

Their scientific advisory committee has recommended, and they have initiated, studies in four areas related to research in aging: dementias, osteoporosis, immune changes and the role of vaccinations, and the general health of older people. Their plans involve comparative studies in a number of different countries, developing as well as developed, of the frequency and underlying risk factors for these conditions.

One striking example is the evidence that dementia of the Alzheimer's type is extremely rare in Central Africa. It may be rarer in China than Japan. We can say the same about the other variables.

Our Institute, through the epidemiology program, is beginning a study in Hawaii of older Japanese who have been followed for many years in the Honolulu Heart Study. We are adding a dementia measurement to this study and have also arranged for a comparative study of Japanese men living in Japan.

We also are developing plans for comparative studies in Hispanic America and Central and Latin America.

LOCATION OF THE OLDEST OLD

Mr. STOKES. Where in the world today do we find the oldest people, here in the United States or in other countries?

Dr. WILLIAMS. I don't think we know. There were fascinating reports from 15 years ago, of very old people in central South America, Villacabamba, and Central Asia, in Soviet Georgia. Those studies were eventually discounted because the birth records were disputed. I honestly don't think we know right now where the oldest people are. It is a very challenging question that we can learn something from.

Mr. STOKES. Sure.

Mr. Conte, I yield to you.

Mr. CONTE. I am going to go roll call.

Mr. STOKES. We will go down and vote and come back.

[Recess.]

ORIGINAL BUDGET PROPOSAL

Mr. NATCHER. Dr. Williams, let me go back just for a moment now in one of our previous questions, the President's original budget proposal last year for research grants, as you know, was $139,000,000. Congress added, we added 9,000,000 to your request for the Institute as a whole. None of that was put into grants; instead, it all went into the centers, and your own in-house activities.

If the problems of low numbers of new grants and downward negotiation are so severe, Dr. Williams, why didn't you use some of those new money for project grants? Why not in project grants, Dr. Williams? Go right ahead, now.

Dr. WILLIAMS. That is a very fair question, certainly, and I want to indicate we had very difficult choices to make, and I regret in some ways that we have not added more money into the research project grants. Our original FY 1990 appropriation contained $142,786,000 for research project grants. This was then reduced by sequestration and other mandatory reductions to $139,697,000. We felt we did have some fairly strong guidelines from Congress, both House and Senate, about areas of priority. It was judged that we should put some of the additional funds into Alzheimer's disease specifically which was done through both research project grants and centers. Additional funds were provided for another Claude Pepper Geriatric Research and Training Center, the rural health and aging center, and the health and retirement survey.

We have a major intramural research on Alzheimer's disease, and a portion of the funds went into this program. As Congress encouraged us to do, we also increased our staffing in both intramural and our support areas to bring us back approximately to our 1983 staffing levels. Another area of Congressional interest was the Alzheimer's Disease Education and Referral Centers, for which funds were provided.

Mr. NATCHER. All right.

ALZHEIMER'S DISEASE FUNDING

Now, Dr. Williams, we have all agreed that Alzheimer's has to be the first priority for your Institute, How much of your budget will be directed to this problem in 1990, and how much in 1991?

Dr. WILLIAMS. In 1990, Mr. Chairman, the total amount expended on Alzheimer's activities is $91,264,000. And in FY 1991, our proposed budget is $94,878,000.

THA CLINICAL TRIAL

Mr. NATCHER. Two years ago, this committee, as you know, provided funds at your request to initiate a clinical trial of a possible drug therapy for these patients called THA, Doctor, as you know. What has been the cost of this trial, and what results are you finding?

Dr. WILLIAMS. The total cost, Mr. Chairman, is approximately $8,900,000, of which NIA has provided $2,800,000, the drug company, Warner Lambert, provided $6,000,000, and the Alzheimer's Association provided $120,000.

We are reaching the end of this trial. It was reviewed by an independent committee several months ago. It was determined that there was enough reason to think that it may be effective and safe, and that the study should be completed with the numbers of sub-

jects originally planned. The completion date of the clinical trial is expected in August of this year.

DRUG TRIALS

Mr. NATCHER. We understand that there are as many as 16 Alzheimers drugs undergoing trial in other countries, particularly in Europe. Should your Institute be more directly involved, Dr. Williams, in drug trials at this time?

Dr. WILLIAMS. I think we should. There are at least two clinical trials that we would specifically like to undertake, depending on the availability of funds. One trial would test acetylcarnitine, which has been tested in Europe, and definitely shown promise. The second clinical trial would test the effectiveness of nerve growth factor, which has, in my judgment, the greatest promise of any treatment for correcting the degenerating and damaged nerve cells.

There are also a number of other drugs. We estimate there are 12 to 16 drugs that may hold promise. These are undergoing initial pilot testing by pharmaceutical firms. Thus it is very likely that these other drugs will reach the phase III stage where the safety and efficacy of the drug should be tested through carefully designed and controlled clinical trial.

SUPPORT FOR CLINICAL TRIALS

Mr. NATCHER. What portion of your 1990 and 1991 budgets is expected to be spent on various clinical trials?

Dr. WILLIAMS. It is approximately $7,500,000 for fiscal year 1990, and about $5,000,000 in fiscal year 1991.

HEALTH AND RETIREMENT SURVEY

Mr. NATCHER. The budget documents that we have before the committee indicates that you plan to renew the longitudinal health and retirement study in 1991. What is the history of this study, and tell us what it would cost, Dr. Williams?

Dr. WILLIAMS. The original Retirement History Survey survey was conducted by the Social Security Administration from 1969 to 1979, when it was allowed to lapse. The research community dealing with both the health and economic issues of aging very strongly holds the view that data obtained from a longitudinal followup of what happens as people move into the retirement, in relation to their health and other characteristics, is extremely important and necessary. We have the support of other Federal agencies, as well as our own, that we should undertake this study.

We plan to award a cooperative agreement to begin the study in September 1990. The annual cost is anticipated to be about $2,000,000.

BALTIMORE LONGITUDINAL STUDY

Mr. NATCHER. Dr. Williams, why isn't the data available from the Baltimore longitudinal study useful in this area? I believe the Baltimore study has been under way for some time; isn't that right?

Dr. WILLIAMS. It is a quite different kind of study. The Baltimore Longitudinal Study of Aging is a study of healthy volunteers; it is not in any sense a population based study. The volunteers return every two years for intensive physiologic tests of all organ systems. Approximately 1,000 active people are enrolled in this study and have contributed to the knowledge we have gained on the course of healthy aging.

The Baltimore Longitudinal Study of Aging wouldn't serve the same purpose as the health and retirement survey, because that survey will be a true population based sample. It will examine the factors dealing with the economics of aging, as well as the general health of the sample population.

Mr. NATCHER. Mr. Conte, I yield to you.

URINARY INCONTINENCE

Mr. CONTE. How about, Doctor, urinary incontinence among the elderly is a major source of anxiety, embarrassment, even social isolation.

Dr. WILLIAMS. Yes, sir.

Mr. CONTE. Over 5,000,000 people suffer from this, at least 800,000 are severely affected to the point of major limitation. We talked about this last year, you and I.

Dr. WILLIAMS. Yes, sir.

Mr. CONTE. What research do you plan to do in this field, and are you looking at prevention and management, and have you made any progress?

Dr. WILLIAMS. We have shown through studies we support that it is in fact possible to correct this problem in more than 50 percent of people who are afflicted by it. Urinary incontinence is one of the three major reasons for admittance to nursing homes. The burden of care becomes excessive at times with this problem, as well as a great social embarrassment and limitation on social activity.

Part of our frailty clinical trials will extend incontinence studies to determine what more we can accomplish in relieving this problem. This has also been a very important area for dissemination of information. We held a major consensus development conference a year and a half ago presenting the results of studies for controlling urinary incontinence. We have published and circulated this information in diverse areas, and it has been, as I understand it, the most sought-after publication that has resulted from any of the NIH consensus development conferences.

Mr. CONTE. I would like to see your publication.

Dr. WILLIAMS. Yes, sir.

DECADE OF THE BRAIN

Mr. CONTE. As you know, the Decade of the Brain is now under way. With all of your work on the brain and the nervous system, your Institute would be an important contributor, I think, to the Decade of the Brain.

Is there any interest on your part to work with the other Institutes on brain-related research?

Dr. WILLIAMS. Absolutely. Dr. Cohen, our Deputy Director, is a member of the committee planning the Decade of the Brain. He is

also the Executive Secretary for the Alzheimer's Disease Council and Panel of the Congressionally-established Office of Technical Assistance. I would like him to comment.

Dr. COHEN. Specifically with regard to the Decade of the Brain, Mr. Conte, an inter-institute committee has been formed, largely of Deputy Directors of the involved Institutes. We are meeting regularly to develop a collaborative agenda in that area. As Dr. Williams mentioned, a major part of our program on Alzheimer's disease is focused on brain sciences. In that area, there is a coordinating council on Alzheimer's disease, which is Department-wide.

NEUROSCIENCE OF AGING

Mr. CONTE. Well, as you know, the neurosciences of aging has profound consequences for medical science. The more we understand about the neurological processes in aging, the better shot we have, I think, in coming up with some kind of a treatment. What is the range of projects that you have got going in looking at the aging process, and the workings of the brain, and what are some of the promising directions in this field?

Dr. COHEN. One of the really fascinating scientific aspects of Alzheimer's disease is that it is a disorder that has brought scientists into the brain as no disorder before it. Extraordinary new findings are emerging, not only offering new clues toward the discovery of the causes of Alzheimer's disease, but also offering new insights about the basic processes of how the brain functions. This new knowledge is from a neurochemical and neuroanatomical standpoint as well as from the vantage point of brain and behavior relationships. Alzheimer's disease really is a paradigm for studying a variety of issues involving brain sciences, as well as for the obvious reason, to crack the mystery around Alzheimer's disease itself.

Mr. CONTE. Dr. Williams, I have a lot—many more questions, we will submit them for the record, and you can answer them as if I had asked them.

Dr. WILLIAMS. Thank you, Mr. Chairman.

Mr. NATCHER. Dr. Williams, we want to thank you and your associates for appearing before our committee at this time on behalf of your budget request for fiscal year 1991. Dr. Williams, it has been a good hearing, and you go back to that one little question in the transcript now and give me a good full answer on that, Doctor, and you and I will continue being good friends.

Dr. WILLIAMS. Yes, sir.

Mr. NATCHER. Thank you, Doctor.

[The following questions were submitted to be answered for the record and the justifications follow:]

RESEARCH MANAGEMENT AND SUPPORT

Mr. Natcher. Doctor, as I think you know, the Committee is concerned about the low number of new grants and the high levels of downward negotiation of both project grants and centers. At least a part of the reason for the shortfall for your programs seems to be related to very large increases for costs within the Aging Institute's internal budget. Can you explain why your research management and support costs increase by 25% in two years?

Dr. Williams. In FY 1990, the Committee provided funds for the Alzheimer's Disease Education and Referral Center (ADEAR) to provide information on this disease to family members, the general public and professionals. I am pleased to say that we now have a contract in place to carry out these activities. Funding for the ADEAR is provided by the Research Management and Support activity. In addition to providing funds for the ADEAR center, Congress also provided us with funds to restore our staffing levels to the FY 1983 levels. A portion of these funds were added to the Research Management and Support activity for additional staff. Other increases in this activity would be associated with mandatory costs.

INTRAMURAL RESEARCH

Mr. Natcher. The cost of the intramural program also is proposed to increase by 18% in two years, from $26 million to $31 million. Why such a large increase in these costs, doctor?

Dr. Williams. The FY 1990 appropriation provided a significant increase for research on Alzheimer's disease. In addition to NIA's extramural support for this research, we also have a strong Intramural Research component. A portion of the increase was provided to enhance the efforts of this group. Further, NIA is also adding subjects to the Honolulu Heart Study to look at the incidence of dementias in the Pacific Basin; funding for this effort is through the Intramural Research activity. As mentioned before, Congress provided funds to restore NIA's FTE level to that of FY 1983; a portion of the funds were added to this activity. Other increases in this activity would be associated with mandatory costs.

ANALYSIS OF CHANGES TO 1990 BUDGET

Mr. Natcher. Doctor Williams, for the record we would like your staff to prepare a detailed analysis of the changes in your 1990 spending plan compared to your original 1990 budget.

Dr. Williams. The following table outlines the changes that occurred to the FY 1990 appropriation.

	FY 1990 Pres. Bud.	FY 1990 Approp.	Mandatory Red. & Sequestrat.	FY 1990 Revised
		($ in thousands)		
Project Grants1/	$139,423	$142,786	-$3,089	$139,697
Centers	21,899	26,866	- 349	26,517
Other Research	9,360	9,360	- 121	9,239
Training	8,301	9,645	- 125	9,520
R&D Contracts	12,177	12,377	- 457	11,920
Intramural Res.1/	27,460	28,582	- 289	28,293
Res. Mgt. & Sup.	11,870	13,893	- 140	13,753
Ext. Construction	0	0	+ 516	516
Total, NIA	$230,490	$243,509	-$4,054	$239,455

_1/ Includes funds for AIDS that had been excluded from the originally submitted President's Budget to make comparable to the FY 1990 appropriation and revised columns.

In making our decisions to allocate funds by mechanism, the National Institute on Aging very carefully analyzed the report language of both the House and Senate Appropriations Committees. The research areas highlighted by both houses of Congress also reflected NIA's own priorities. We thus provided increases to research project grants, research centers, research training, R&D contracts, intramural research and research management and support. These increases provided funding for Alzheimer's research, special populations such as the oldest old, minorities and rural elderly, research training, training supported through the Claude Pepper Geriatric Research and Training Centers which also have an Alzheimer's research component, the Alzheimer's Disease Education and Referral Center, and restoring NIA's FTE level to that supported in FY 1983.

After these decisions were made, NIA was instructed to make reductions in its budget, as were all NIH institutes, centers and division, according to Congressional language. These reductions were for capping the principal investigators salary on grants and contracts at $120,000, procurement reductions, an extramural construction tap, and a salaries and expense reduction. Such reductions were taken in the appropriate mechanisms. In addition, sequestration also called for further reductions which were mandated to be taken across the board on all mechanisms and on all programs, projects and activities (PPA) that were specifically identified in report language. The exact definition of the PPAs was determined by the Department of Health and Human Services, and for this, the Senate language was used since it had more specific earmarkings.

In making its decisions on how to best take the cuts and to minimize reducing the number of competing research project grants (RPGs), NIH made the decision to increase the downward negotiations so that the number of competing RPGs could remain essentially the same as planned in the FY 1990 Appropriation. For the National Institute on Aging, that meant keeping the number of competing RPGs at 156 while increasing the downward negotiations from the planned 12 percent for noncompeting awards to 13 percent and the planned 10

percent for competing awards to 15.5 percent. In addition, since NIA gives importance to RPGs, we made the difficult decision to reduce our Centers awards by approximately 18 percent across the board in FY 1990 so that we would not have to reduce our research project grants any further.

INCREASE IN NEW GRANT APPLICATIONS

Mr. Natcher. Doctor, one last question. The budget tables submitted by the Department indicate that you expect a large increase in the number of new grant applications to be submitted in both 1990 and 1991. As you know, this number has not increased in previous years. What is the basis for your current estimate?

Dr. Williams. The Congressionally mandated Advisory Panel on Alzheimer's Disease, in its report released last year, stated, "Biomedical research offers the only hope for curing and for preventing Alzheimer's disease and related dementias (ADRD). Rapid advances have been made in solving the mysteries of these disorders, and the biomedical research field is poised for significant breakthroughs, given adequate resources. Fortunately, the Nation has a cadre of well trained scientists who could potentially enter this field..." Since the release of this report, NIA staff have very aggressively pursued announcing the report and its recommendations to scientists in the field as well as in related fields. NIA also plans to announce a series of Requests for Applications to increase the overall effort in Alzheimer's disease, which is one of this country's most devastating diseases, affecting approximately 4 million Americans and costing over $88 billion annually. Other staff efforts, as well as those of academic research leaders, are directed at increasing research in other priority areas such as physical frailty, including osteoporosis and hip fractures, rehabilitation, pharmacology in aging and long-term care. It is through such efforts that NIA anticipates an increase in the number of new grant applications.

NUTRITIONAL NEEDS

Mr. Conte. Addressing the nutritional needs of the elderly is basic to the health and welfare of our senior citizens. A significant portion of the elderly are in situations where they receive poor nutrition. Are you looking at how metabolic changes involved in the aging process affects nutritional needs?

Dr. Williams. Except for certain subgroups such as the economically disadvantaged and chronic alcohol abusers, epidemiologic evidence indicates that most non-institutionalized older people do not have clinical signs of undernutrition. Intakes of most nutrients except calcium, vitamin A, thiamin, riboflavin, and iron approach or exceed the recommended amounts for persons over 50 years of age. However, data are sparse on people aged 75 and over, who appear to be at greatest risk for poor nutrition. Thus, a significant number of community-dwelling older people remain at risk for poor nutrition.

Even in the absence of clinical deficiency symptoms, the average serum levels of several nutrients including vitamin D and folate are lower in older age groups than in younger adults. One of the goals of NIA's nutrition research program is to determine the extent to which age-related changes in nutrient concentrations in blood and other tissues may reflect subclinical deficiencies of body stores that increase the risk of illness and chronic diseases common in old age. To determine this we need research to establish nutritional standards and measures for older people, especially the oldest old, for whom we have almost no nutrition information.

In contrast to the free-living population, between one-third and two-thirds of older persons requiring hospitalization or long term care facilities have signs of protein-calorie malnutrition (PCM). Symptoms include rapid weight loss, emaciation, loss of appetite, dehydration, confusion and a loss of blood proteins. Nutritional status at the time of admittance is an excellent prognostic indicator of both morbidity and death in older people. The NIA is supporting research to decermine whether PCM in older people is a syndrome in its own right or occurs secondary to other diseases. Concurrently investigators are trying to find ways to improve nutritional support systems that will improve or restore the nutritional status of older patients.

NIA researchers are also investigating the metabolism of lipids and fat soluble vitamins A, D, E, mineral homeostasis, and B vitamin metabolism in older people. A number of studies are investigating the causes and consequences of changes in body composition--lean body mass, adiposis tissue, bones, and water--and the risk of chronic disease with the redistribution of fat from the limbs to the trunk that usually occurs with age.

Mr. Conte. What research are you doing that could improve the nutritional status of the elderly?

Dr. Williams. In FY 1989 the NIA funded 67 grants for a total of $8.5 million. Of these awards, 43 percent were metabolic

studies, 19 percent were cell biology, 19 percent were clinical investigations, 12 percent were epidemiological, and the remainder--7 percent--were behavioral studies.

The NIA supports studies on the changing requirements of older people for energy--including calorie restriction in animal models--protein, calcium, zinc, copper, and vitamins A, and D, thiamine, riboflavin, folate, vitamin B6 and Vitamin B12. Other studies concern changes in the metabolism of lipids, including cholesterol, carbohydrates, and aluminum and how they change as risk factors for chronic diseases with age.

These studies are particularly timely since the Tenth Edition of the National Research Council's Recommended Dietary Allowances (RDA's), released in the fall of 1989, give only one set of recommendations for all men and one set for all women over for age 50 years of age. Though the RDA Committee acknowledged that older people may have altered requirements, they concluded, "the data are insufficient to establish separate RDA's for people over 70 years of age." In addition, recommendations for those over 50 years of age are extrapolated from those of younger age groups.

Mr. Conte. What opportunities are there in this field?

Dr. Williams. The mission of the NIA is to foster research that finds methods to extend years of productive life through improved health, lifestyle, and psychosocial status. If sufficient funds are available, the NIA's Nutrition and Aging Program can contribute to this goal by sponsoring studies to determine the ways that nutrition influences the onset and progression of aging and diseases of old age.

Specific topic areas of opportunity include:

- Nutrient requirements and their age-dependent requirements in older people and animals including determinants of nutrient homeostases with aging and the role of nutrients and other components of foods in neurologic function.

- Effects of age on physiological processes through which nutrients, drugs, and other non-nutrient substances are absorbed, metabolized, and excreted in humans and in analogous animal models.

- Factors and mechanisms responsible for age-related changes in energy--calories--utilization including effects of caloric reduction on longevity and maintenance of functions and of caloric excesses resulting in premature mortality and pathologies of old age.

- Nutritional factors associated with physiologic changes such as immunocompetence, neurologic function, body composition, sensory perception--chemical senses and taste and smell--control of appetite, macronutrient storage and utilization, rheology, otolaryngology, endocrine control, and genetics.

- The role of nutrition factors in prevention and treatment of age-related degenerative diseases, including diabetes, osteoporosis, neurologic disorders, immune deficits, heart disease, cancer, gastrointestinal diseases, problems of the oral cavity cancer, and kidney diseases.

- The reciprocal effects of nutrition on age-related disorders of the gastrointestinal tract (GI) including chronic atrophic gastritis, hypochlorhydria, diverticulosis, and GI enzyme and hormone disorders.

- The role of free radical damage, glycation and other post translational modifications on aging and diabetes.

- Psychosocial aspects of nutrition, including studies of diet as a major factor contributing to the quality of life and how diet interacts with other lifestyle variables, including exercise, smoking, and consumption of alcoholic beverages.

- Nutritional status of older Americans and subpopulations of older people at special nutritional risk.

- The influence of genetic variation, race and gender on nutrition and aging.

- Identification of nutritional factors that can retard aging processes and/or prevent, mitigate, or reverse age related pathology.

- Educational methods and program strategies that best promote adequate food consumption and avoid harmful dietary practices by older people.

PRESSURE SORES

Mr. Conte. Doctor, pressure sores are a common, preventable complication for elderly people who are hospitalized for a long period of time. This problem is well known in the medical community, but progress seems to be slow. What projects are underway to see what preventive measures can be taken to avoid pressure sores?

Dr. Williams. A project conducted at an NIA-supported Teaching Nursing Home in Boston, Massachusetts has studied a data base of 20,000 institutionalized residents across the U.S. to examine the epidemiology, healing, and risk factors for pressure sores among institutionalized older persons. NIA currently supports a prospective study of 1,300 bedridden older patients in an acute general hospital. This study aims to define the risk factors causing pressure sores and the consequences of these sores on morbidity and mortality. Extensive clinical and nutritional data is being collected on admission of the patients. At the present time, preventive measures do seem to be the best approach to this problem although the expected development of new agents which promote wound healing offer additional promise for the future.

Mr. Conte. What is known about the underlying biological mechanism involved in pressure sores?

Dr. Williams. Prolonged immobility causes occlusion of blood vessels by mechanical pressure. The resulting loss of blood flow deprives tissues of oxygen and nutrients and prevents the removal of toxic metabolites. This is why repositioning of patients, which allows restoration of blood flow to tissues, is so important. Other factors involved in the breakdown of skin include shearing forces, friction, moisture and a deficiency of Vitamin C and other nutritional elements which may act as predisposing factors for the formation of pressure sores in older persons.

BIOMARKERS

Mr. Conte. What can be learned from biomarkers in aging research?

Dr. Williams. Biomarkers of aging will provide the only practical approach to testing interventions in aging processes. They will allow us to judge the rate of aging in less than the lifetime of the individual so that, for example, an intervention in a human clinical trial could be tested in 5 to 10 years, rather than the 75 to 115 years that would be needed to observe lifespan extension without such a measure. In addition, the research being done to develop biomarkers of aging is providing a great deal of information about normal aging development and about individual differences in patterns of aging. This information will vastly improve our understanding of "normal aging." Finally, as a part of this research, we have included studies of the effects of dietary restriction, which is currently the only intervention known to increase lifespan. Understanding how dietary restriction produces this effect and finding biomarkers that anticipate the increase in lifespan will provide very important information about basic aging processes.

Mr. Conte. What are the applications of the PCR reaction in your research?

Dr. Williams. The Biomedical Research and Clinical Medicine Program of the National Institute on Aging supports several scientists studying the fundamental mechanisms which govern biological aging. Age-dependent changes in the regulation of cell proliferation and maintenance of differentiated cell function are important areas of current research. The polymerase chain reaction (PCR) is being used to amplify regions of DNA from old cells believed to be involved in age-specific changes in cell proliferation and differentiated cell function. Molecular cloning of critical regulatory genes is facilitated by PCR-mediated DNA amplification. PCR is also being employed in the characterization of regulatory elements and proteins responsible for age-dependent changes in gene expression.

DRUG COMPLICATIONS IN THE ELDERLY

Mr. Conte. As the body ages, the internal processes change to the point where certain drugs may cause adverse reactions. Certain

drug combinations which cause no harm in younger people can be deadly for the elderly. With the thousands upon thousands of medicines on the market and the literally millions of potential drug combinations, there is clearly a need for this type of research. What is the extent of your research in preventing drug complications in the elderly?

Dr. Williams. Research aimed at reducing drug complications is a major NIA priority. This research has already produced several important findings. For example, an NIA-supported study conducted in Nashville, which recently appeared in the Journal of the American Medical Association, showed that use of some tranquilizers, but not others, was associated with higher rates of falling leading to hip fractures in older persons. This information could be translated directly into better drug prescribing. Since the annual cost of hip fractures exceeds $7 billion, a decrease of only 15 percent resulting from better prescribing would save over $1 billion in health costs, not to mention reductions in disability. Another NIA-supported study by San Francisco researchers showed that one anti-ulcer medication commonly used by older persons increases the risk of fainting and falls in those also taking certain blood pressure medications, whereas another anti-ulcer drug did not have this effect. These are only two examples of numerous previously unrecognized drug effects which could be revealed by this type of research, which could lead to significantly improved geriatric care and lower unnecessary health costs, especially among frail older persons.

Mr. Conte. Are we doing enough in this field? What are some of the promising research opportunities?

Dr. Williams. I believe the current extent of research only addresses a small fraction of undiscovered drug effects and interactions in older persons. Bearing in mind that the use of medication is the most common medical treatment, a greatly expanded effort in this area is needed. Promising additional opportunities in this field include the development of new medications for age-associated diseases and techniques to improve physicians' prescribing practices and patients' use of drugs. There also is a need for research-based guidelines for the withdrawal of medications from older persons so that only those medications required are continued.

NIA has issued a Request for Applications: "Pharmacology in Geriatric Medicine," which solicits research on these topics, to be funded in FY 1991. Over 100 applications have been received. We expect that resources will permit funding only approximately eight of these projects. We believe that this pharmacology initiative is a very important part of NIA's overall program to reduce frailty and its complications among older persons.

HIP FRACTURES

Mr. Conte. Elderly Americans have collectively spent over 3 million days in the hospital because of hip fractures. The cost to care for these people runs into the billions. A report out of your

institute suggested that the use of a certain hypertension drug (Thiazide) was associated with a 30% decrease in hip fractures among the elderly. What might account for this finding--is it related to the fact that this drug reduces calcium losses by the kidney?

Dr. Williams. Preservation of bone strength and resistance to fractures is dependent on the preservation of bone calcium. Administration of thiazide diuretics has been shown to decrease urinary calcium loss, leading to an improvement in calcium balance. As you suggest, this decreased calcium loss is thought to be the likely explanation for the reduction in hip fractures in patients taking thiazides. Further studies are needed to determine the relative risks and benefits of thiazides for specific groups of patients at risk for osteoporosis and cardiovascular disease, as well as the indirect effects of thiazides on other factors affecting bone loss, such as vitamin D status.

Mr. Conte. A recent study also linked decrease in bone mass with a greater incidence of hip fractures. There are numerous preventive measures to reduce osteoporosis. Are you engaged in outreach efforts to improve education of people at risk for hip fractures and to teach them preventative measures?

Dr. Williams. NIA's Information Office has used various dissemination activities to reach people at risk for hip fractures:

- Wrote articles for various magazines that reach press, professional, and lay publics. This includes my regular column in the National Osteoporosis Foundation Newsletter and an article on falls for the NIH magazine.

- Issued press releases on the newest research findings. Most recently, NIA issued a press release on Fall-Safe, an intervention device for older people that reduces the force of falls and another on the increase of the incidence of falls with certain medications.

- Distributed at national conferences fact sheets, "Osteoporosis: the Bone Thinner," "Prevention of Falls and Fractures" and "Accidents and the Elderly" published by the Information Office.

- Arranged for NIA staff to appear on TV and radio talk shows. Recently I appeared on the Today Show to talk about hip fractures.

- Developed a public service pamphlet in conjunction with the Human Nutrition Information Service of USDA which is designed specifically to assist older people in implementing the DHHS/USDA Dietary Guidelines for Health Americans. Information is provided on the relationship of diet and exercise to osteoporosis. This pamphlet will be distributed with the USDA "Mini-Bulletin" series and through national channels developed by NIA.

HEALTH AND RETIREMENT SURVEY

Mr. Conte. The Congress directed that a study, The Health & Retirement Survey, be started to track a cohort of people and their future health and financial status over the years. What is the status of this survey?

Dr. Williams. The National Institute on Aging has issued a Request for Application calling for a Cooperative Agreement for the Health and Retirement Study. The study will begin in September 1990. We expect that the design and planning phase should last about a year. If the baseline interview is in 1991 and 1992, the first results would be available in late 1992 or early 1993. The Institute budget does not include funds for this project in FY 1991.

Mr. Conte. Are there sufficient funds in this budget for this project?

Dr. Williams. Congress provided $500,000 for the first phase of the study. The basic study is estimated to cost $2 million per year after the design phase, of which $550,000 is included in the budget.

SLEEP DISORDERS

Mr. Conte. Over half of all people over 65 suffer from some form of sleep disorder. The lack of proper sleep disrupts the quality of life of the senior citizen, but it can also disturb the livelihood of family members as well. Can you tell us what is being done in the area of sleep disorders among the elderly?

Dr. Williams. Disorders of sleep are estimated to afflict over half of the people 65 and older who live at home and about two thirds of those who live in long-term care facilities. Problems in nighttime sleep and daytime wakefulness disrupt not only the older persons' lives but also those of their families and caregivers. While most sleep disorders are not life-threatening, they have serious impacts upon lessening the quality of life for both the older person directly affected as well as the quality of life of those others in the household of that person. It is now estimated that sleep problems are a major cause of institutionalization into long-term care facilities, as are problems dealing with restricted mobility and incontinence. In one study, insomnia was the strongest predictor of both mortality and nursing home placement for older males.

It is necessary to understand the causes of these disorders and to develop better treatment strategies, including non-pharmacological methods, to alleviate these problems associated with later life. The NIA is a major supporter of sleep research at the NIH. In FY 1989, it allocated an estimated $4 million towards the support of sleep research. The NIA is committed to the further stimulation of research on the epidemiology, treatment, and etiologies of these sleep disorders. In FY 1990, the NIA issued a request for proposals dealing with geriatric pharmacology which also addresses the question of the pharmacological treatments of sleep

disorders, such as insomnia, in the older population. In addition, the NIA just sponsored an NIH Consensus Development Conference on the Treatment of Sleep Disorders of Older People in order to reach agreement on determining what changes in sleep are clinically important, how they are best diagnosed and treated, and how the public can establish good sleep practices. The NIA also is planning on supporting an international symposium on Sleep and Respiration in Aging Adults in FY 1991. Both of these major conferences will provide important now insights and recommendations for new research directions that need to be developed.

DRUG ABUSE AMONG THE ELDERLY

Mr. Conte. What is known about the extent of drug abuse, either with prescription or illegal drugs, among the elderly?

Dr. Williams. Overuse of prescription medications is a serious problem among older persons, although medications are of immense benefit for treating diseases. The use of illegal drugs, while a significant problem, is generally less common in the elderly than is the inappropriate use of prescription drugs.

Adverse drug side effects are a special problem among older people, since they are more likely than the young to consume prescription drugs, to have complex drug regimens, and to be seen by a large number of health care providers. Recent research shows that many drug side effects are unrecognized by both patients and their health care providers. There is also a communication gap between patients and their doctors, with patients not understanding or not being told about the detection and management of side effects.

Mr. Conte. Are additional studies needed?

Dr. Williams. Though we have already learned much about ways to improve physician prescribing and proper use of medicines by patients, we still need to learn better ways of applying these approaches to the complex challenge of geriatric drug prescribing. Older persons are especially vulnerable to the side effects of medications and commonly take multiple medications, which greatly complicate the picture. As we learn more about new drugs, drug side effects, drug interactions, and other factors which relate to good prescribing and medication use, we need to learn how best to translate this knowledge into common practice.

PREVALENCE OF ALZHEIMER'S DISEASE

Mr. Roybal. Recent research findings from a study in East Boston suggest that as many as 47% of people over age 85 may have Alzheimer's disease. What implications does this finding have for the future?

Dr. Williams. The report of the prevalence of Alzheimer's disease by Dr. Denis Evans and colleagues has caught the attention of the general public as well as the scientific community. The paper did, indeed, reveal higher prevalence rates at all age groups than previous investigations. The immediate implications of these data, when extrapolated to the United States population, are that the extent of AD in our population is much greater than previously appreciated. If it is assumed that the rates from East Boston accurately reflect the experience of the rest of the United States, then as many as 4 million people may already be suffering from this disease.

Alzheimer's disease is clearly most common in very old people, those over 85 years of age and older. It is even more common than previously appreciated. The numbers of people over 85 are growing faster than other segments of our society, and therefore, the number of individuals afflicted with AD will continue to increase. The immediate and future implications of these trends will have a major impact on the families involved and on health-care costs and the resources necessary to take care of these increasing numbers of people. The most important implication, in my judgement, is that we must stop this disease through adequate research.

Mr. Roybal. What significance does this huge change have for Federal research policy?

Dr. Williams. Alzheimer's disease is a serious public health problems facing our country. AD not only affects an enormous number of people, but it also has a very long course. We now hear reports of people surviving for 20 years with Alzheimer's disease. The destruction of the life of the afflicted people and the consequences to the families and caregivers are extraordinary.

Mr. Roybal. What is the incidence of Alzheimer's disease in the population aged 40-65? Are we seeing any increased incidence of Alzheimer's disease in younger populations, 40-50 years old?

Dr. Williams. Very little data exist on the annual occurrence of new cases of Alzheimer's disease in younger populations. Alzheimer's disease is primarily a disease of later life. To our knowledge, there have been no population based surveys of the incidence of Alzheimer's disease at very young ages. There are so few cases that the cost of population based research would be prohibitive. It is certainly true that AD does on occasion occur in persons in their 40s and 50s and that major tertiary care medical centers do see such relatively young AD patients. At this time, there is no scientific evidence to suggest any change in the rates at which the disease occurs in this age group.

NEW DRUGS FOR ALZHEIMER'S DISEASE

Mr. Roybal. Dr. Williams, it is my understanding that there are as many as 16 new drugs that may help in treating Alzheimer's disease patients, yet only one drug, THA, is being tested in this country. All the rest are undergoing clinical trials in Europe. It troubles me to think that more people may suffer, simply because we have not devoted enough resources to testing some of these and other promising drugs. Why is it that the NIH has not funded more clinical trials?

Dr. Williams. It is only within the last 10 or so years that significant research attention has been directed to AD. Research efforts stimulated by the NIA are proving to be the basis for the development of new treatments for AD. The race to find a definitive treatment for Alzheimer's disease (AD) is clearly underway. It was estimated by a recent national survey that over 100 trials, controlled and uncontrolled, have been conducted with drugs for the primary and secondary symptoms of AD. As many as 40 existing drugs, compounds, and biologicals have been proposed or suggested as treatments for AD, and there are now 16 pilot or preliminary studies of drugs for AD underway in the United States, some of which are likely to indicate the need for full scale clinical trials. Through the 15 funded ADRCs, we have begun to lay the infrastructures for drug development and testing. We are also actively pursuing collaborative efforts with the pharmaceutical industry. Recently, NIA sponsored a planning conference to identify new strategies for the treatment of AD.

Mr. Roybal. Would you describe some of the drugs you feel most hopeful about?

Dr. Williams. As you know, NIA is currently testing the safety and efficacy of THA, and we hope to have the results of this trial by late summer 1990. The current generation of potential treatments focus upon the replacement of transmitter deficits found in AD. New generations of treatments will focus upon nerve growth factors, calcium channel blockers, metabolic enhancers, transport mechanisms for the efficient delivery of drugs, and regulators of gene expressions.

Currently, there are 16 drugs in various stages of pilot or preliminary study for the treatment of AD. One of these, acetyl-l-carnitine, has proved effective in improving memory in animal studies. The precise mode of action is not known. It has been shown to have some cholinomimetic action, but more importantly it seems to improve mitochondrial metabolic activity. There is an accumulation of evidence that AD may be a reflection of a systemic metabolic effect due to specific defects in mitochondrial enzyme systems. Acetyl-l-carnitine has been shown to stabilize the cognitive functions of AD patients over a 12-month study period.

Another drug under preliminary study is nimodipine. Nimodipine is a calcium antagonist, approved for the treatment of strokes, that may prevent membrane changes which interfere with learning. Preliminary evidence from aging rabbits and from people suffering

from strokes, indicates that nimodipine may improve memory and possibly restore cognitive function.

Studies in animals indicate that nerve growth factor (NGF) can prevent injury-induced degeneration of cholinergic neurons and improve cognitive functions. NGF may prove to be a valuable treatment alternative for AD. The NIA held a workshop in 1988 on the possible use of NGF in the treatment of AD. Among the conclusions of that workshop were that before human trials are initiated, further preclinical studies in non-human primates are needed to determine toxicity and drug delivery systems, as well as that a reliable source of well-characterized NGF be made available. In light of the progress towards achieving these ends, the NIA is planning to hold another workshop this year to reconsider the status of NGF as a potential treatment for AD.

Huperzine-A is a novel alkaloid compound isolated from the plant Huperzia serrata, the leaves of which have long been used in China as a "memory tea" prescribed by herbalists for failing memory. This compound has now been synthesized. It appears to function as a highly efficacious cholinesterase inhibitor; it increases the action of acetylcholine by retarding its enzymatic degradation as does THA. Since huperzine-A has been investigated in double-blind trials in China for the treatment of AD and reported to be efficacious, serious consideration should be given to the biological, safety, and behavioral assessment of this agent in this country.

INCREASED FUNDING FOR ALZHEIMER'S DISEASE

Mr. Roybal. If this subcommittee were to provide you with $300 million for FY 1991 as proposed in the CARE bill introduced by myself and Representatives Waxman and Stark, please detail, in priority order, the areas in which the money could be best spent.

Dr. Williams. There are a number of very important avenues in Alzheimer's disease research that would be pursued more vigorously if additional funds were made available. First, the cause(s) of Alzheimer's disease, including studies of membrane structure, function, and transport mechanisms in the aging central nervous system is extremely important. A particularly vital area is understanding the mechanisms underlying the selective neuronal cell death in Alzheimer's disease. The special vulnerability of the aging central nervous system to infectious agents, internally produced toxins, and externally introduced toxins requires increased investigation. It is particularly important to examine the effects of long-term low level exposure to specific agricultural herbicides and pesticides.

Better diagnostic techniques, including an easy and reliable biochemical diagnostic technique for AD, is another priority area. Research is ongoing and several promising leads have appeared. The most useful type of diagnostic tool would be a simple blood test, either for serum proteins or biochemical defects in blood cells. Exciting new findings indicate that early in the course of AD there are reductions in the metabolism of brain cells in the areas involved in the regulation and control of attention. Impairments of attention may prove to be a very early marker for AD and may be

amenable to pharmacologic interventions. Another exciting possibility being investigated is that blood or skin cells of AD patients may show the same biochemical defects that appear in neurons; if this proves consistently true, it would give us an early marker for AD.

Another critical area is development of new treatment and management methods, including the discovery of pharmacologic or biological agents that will safely, reliably, and effectively retard the progress or permanently interrupt the relentless course of AD. Clinical trials on such agents as acety-l-carnitine and nerve growth factor should be undertaken as soon as feasible.

Cross-cultural and cross-national epidemiologic studies, including the study of population groups with varying genetic compositions, exposures, occupations, and life styles will provide important clues of the etiology of Alzheimer's disease. Examination of different people with different characteristics and histories may reveal risk factors for AD, which will suggest new testable hypotheses on its origin. There is also very important work needed in the development of new screening and diagnostic assessment procedures to support epidemiologic studies.

Alzheimer's Disease Research Centers (ADRCs), including the development of satellite diagnostic and treatment centers and Alzheimer's Disease Center Core Grants add an important dimension to AD research. The Alzheimer's Disease Research Centers are the foundation of the NIA efforts to develop a national AD research program. To complement the work of the ADRCs, the AD Center Core Grants will provide core facilities and resources upon which scientifically meritorious research programs can be constructed. The ADRCs also need to be brought to full funding to maximize their research productivity and research training potential.

NIA is expanding its intramural research program at the Gerontology Research Center to address the basic biology of AD, with development of a laboratory specifically devoted to molecular neurobiology.

The Leadership and Excellence in Alzheimer's Disease (LEAD) award has been very influential in focusing additional attention on the importance of research in AD and in training the next generation of scientists.

One of the most critical needs of investigators is a stable source of carefully characterized normal aged and AD post-mortem brain tissue. A national shared tissue resource is being developed through the ADRC program, but could be expanded to be of great assistance nationwide.

As Congress directed, the NIA has developed a central national information resource, the Alzheimer's Disease Education and Referral Center, that will identify, catalog, and provide public press and media and scientific material on Alzheimer's disease to patients, family members and the scientific and medical communities.

Part of our mission is to develop and distribute nationwide educational and training materials through the Alzheimer's Disease Research Centers for direct care providers and ancillary personnel, such as home health aides, nursing assistants, homemakers, police and ambulance attendants who often come in contact with AD patients in emergency situations.

The burdens of care for AD patients are now well-documented. The need for appropriate services and quality care will intensify as the numbers of older people, and especially those 85 years and older, continue to grow rapidly. Especially needed is the development of a knowledge base for planned social, behavioral, and technological interventions that can make a difference in the daily life of caregivers.

PROMISING RESEARCH IN ALZHEIMER'S DISEASE

Mr. Roybal. In what promising research areas has NIA been unable to launch an appropriate effort because of inadequate funding?

Dr. Williams. While the NIA has attempted to fund some applications in all promising areas, a very large number of excellent applications in virtually every arena have gone unfunded.

Mr. Roybal. What funding levels would be required to take real advantage of the most promising avenues of productive research, while ensuring that the money would be spent wisely?

Dr. Williams. In my professional judgement, an additional $77 million will allow NIA to take advantage of current promising avenues of research. This, when added to NIA's current projection of $94,878,000, would bring NIA's funding to $172,000,000 for Alzheimer's disease research.

DIAGNOSTIC TEST FOR ALZHEIMER'S DISEASE

Mr. Roybal. How close are we to finding a definitive diagnostic test for Alzheimer's disease?

Dr. Williams. Research to develop an easy and reliable biochemical diagnosis for AD is ongoing, and several promising leads have appeared. The most useful type of diagnostic tool would be a simple blood test, either for serum proteins or biochemical defects in blood cells. Currently, attempts are underway to detect in the serum of AD patients the breakdown products of proteins that accumulate in the brain. Preliminary experiments have detected Alzheimer's disease specific proteins in the cerebrospinal fluid of some patients. An exciting possibility being investigated is that blood or skin cells of AD patients may show the same biochemical defects that appear in neurons. Recently, it was reported that accumulations of protein similar to the amyloid protein deposited in AD brain were found in the skin of AD patients. This observation could lead to a skin test for AD. Other metabolic differences have been sought between normal cells and cells from AD patients.

Possible changes have been reported in mitochondrial enzymes and also in the enzymes that regulate cell metabolism by the addition or removal of protein phosphates. The proteolytic enzymes, which seem to be centrally involved in AD, may also be altered in other cells of the body, but this has not yet been investigated. Identification of one or more defective genes in families with an inherited pattern of AD would lead to straightforward blood tests for AD. Magnetic resonance imaging (MRI) also shows promise as a diagnostic tool for Alzheimer's disease. Patients examined early in the course of the disease showed elevated levels of certain neuronal membrane precursors that were easily detected by MRI. Prospects for the development of blood, skin, or imaging diagnoses are very good, but considerable research is required. Especially problematic is the slow progression of the disease, which makes any disease-specific changes likely to be subtle. Nevertheless, the exquisite sensitivity of modern biochemical and imaging techniques allows even very small differences to be reliably detected. These differences must only be determined to be truly specific for the disease, and to appear early in its course.

BIOLOGICAL MARKERS FOR ALZHEIMER'S DISEASE

Mr. Roybal. How close are we to identifying biological markers to assist the medical community in early identification and treatment of Alzheimer's disease?

Dr. Williams. As I just mentioned, we have several very promising leads for identifying biological markers of Alzheimer's disease. For example, if the mitochondrial enzyme defect proves consistent and true, this would open the door for several new strategies for treating Alzheimer's disease.

TREATMENT OF ALZHEIMER'S DISEASE

Mr. Roybal. What is the status of research investigating therapeutic approaches and treatment of Alzheimer's disease?

Dr. Williams. The effort to develop new treatment and therapeutic approaches is a major programmatic initiative of NIA and is being vigorously pursued from the perspective of not only trying to develop new pharmacological treatments for AD, but also work on finding behavioral and psychological approaches for managing the secondary symptoms of Alzheimer's patients. At present, there are no major breakthroughs to report. Most work is in its early preliminary stages.

MULTI-CENTER CONSORTIUMS FOR ALZHEIMER'S DISEASE

Mr. Roybal. Please identify the 20 institutions who are funded as the multi-center consortium for Alzheimer's Disease or CERAD.

Dr. Williams. The Consortium to Establish a Registry for Alzheimer's Disease or CERAD was awarded to Duke University with Dr. Albert Heyman as the Principal Investigator. The participating sites are Baylor University College of Medicine, Burke Rehabilitation Center-Cornell, Columbia University--Presbyterian Hospital, Duke University Medical Center, Emory University School of

Medicine, Johns Hopkins Medical Center, Massachusetts General Hospital, Mt. Sinai Medical Center, University Hospitals (Cleveland), University of Alabama Hospital, University of California, University of Iowa, University of Kentucky, University of Pittsburgh, University of Rochester, University of Southern California, Southwestern Medical Center, University of Washington, Veterans Administration Hospital (Minneapolis), and Washington University.

Mr. Roybal. Do these centers include persons of racial and ethnic minority groups in their research and data collection?

Dr. Williams. The large majority of cases enrolled thus far are white, well-educated persons with mild or moderate dementia. Additional enrollment of such patients is not needed. In order to achieve a more representative sample, CERAD is now recruiting Blacks and native Spanish-speaking patients, as well as white patients with less than 9 years of formal education. Since many of the native Spanish-speaking older people in the U.S. are not fluent in English, the clinical and neuropsychological assessment batteries have been translated into Spanish. Incorporation of large numbers of minority group members is a major initiative for CERAD during the next five years of research work. One of the criteria for becoming a CERAD participating site is the ability to recruit minority group members and the operation of ongoing community outreach programs. In addition to the CERADs, the NIA is establishing satellite clinical centers in conjunction with the Alzheimer's Disease Research Centers that will reach out to rural, inner city and minority areas.

Mr. Roybal. What have we learned from CERAD?

Dr. Williams. CERAD participants developed standardized instruments for assessment of the clinical, neuropsychological, neuropathological, and neuroimaging components of AD. They organized a large carefully monitored data bank that now contains some 640 cases and 430 control subjects enrolled from the 20 university medical centers in the U.S. Cognitive function has been measured in AD patients and controls at entry and at annual return visits. CERAD has changed the routine assessment of AD patients in the U.S. and has improved the level of diagnosis nationwide.

Mr. Roybal. In your professional judgement, what would be an appropriate funding level for their research studies?

Dr. Williams. There are many other efforts underway by CERAD, including the incorporation of international sites with the accompanying translation and standardization studies, the development of a family pedigree study, which is important for the investigations of familial AD, and a national survey of clinical experience in and resources for therapeutic trials of drugs for AD.

The funding for CERAD for FY 1990 will total approximately $950,000. The level of effort and breadth of CERAD could be doubled to $1,800,000 per year and remain scientifically efficient. This project is one of the most productive and influential ones ever funded by the NIA.

INTERNATIONAL COMPARATIVE STUDIES OF ALZHEIMER'S DISEASE

Mr. Roybal. Is the NIA involved in any international comparative studies or scientific exchanges related to Alzheimer's Disease? What is the potential value of such international efforts.

Dr. Williams. The NIA is involved in a number of cross-cultural and cross-national studies of AD and other dementias of later life. The NIA, in conjunction with the World Health Organization Special Program of Research on Aging, is developing an epidemiological study of dementias and Alzheimer's disease in five countries, including Spain, Chile, Malta, Nigeria, and Canada. The coordinating center is located in Florence, Italy. This study will provide important new data on the prevalence of AD and other dementias in very different populations and cultures worldwide. A major effort is just now getting underway in Hawaii and is aimed at the accurate assessment of rates and patterns of dementia among older Japanese-American men. A great deal of care will be taken in this study to ensure that its findings can be compared with other studies that are being or have been conducted in Japan, Taiwan, and the Continental U.S.

International and cross-cultural epidemiologic studies are extremely important. Older people in the U.S. and in many other countries are very heterogeneous. They come from many ethnic and genetic groups and have an enormous number of different life styles, experiences and exposures. We do not know how any of these factors are related to the likelihood of developing Alzheimer's disease. It is not yet clear whether different subgroups of older people have differing rates of AD or whether AD rather uniformly affects older people. Variations in age-specific incidence rates may lead us to ideas about risk factors and to new testable hypotheses about the origin of AD.

CLAUDE D. PEPPER CENTERS

Mr. Roybal. How many Claude D. Pepper Geriatric Research and Training Centers has NIA funded? How many effective centers could be funded at this time?

Dr. Williams. There are currently two NIA Claude D. Pepper Geriatric Research and Training Centers. At least five high quality projects could be funded if funds were available. The average cost for each of these centers is $1.2 million per year and thus would require an additional $6.0 million in FY 1991.

Mr. Roybal. What are their functions?

Dr. Williams. The major function of these centers is to create an environment for the career development of the next generation of academic leaders in geriatrics. These academic geriatricians will then be available at institutions across the country for the training of clinical geriatricians who will provide health care to the growing population of older persons. The current shortage of well-qualified academic leaders in geriatrics severely limits the capacity to train these clinical personnel. Because of this, the

Institute of Medicine in 1987 recommended the creation of "centers of excellence" to train academic leaders in geriatrics. Accordingly, the National Institute on Aging (NIA) created the Claude D. Pepper Geriatric Research and Training Centers program. These centers provide a rich environment to develop teaching, research and clinical skills in future academic leaders in geriatrics.

LONG-TERM CARE

Mr. Roybal. What long term care research initiatives are currently funded or proposed for funding by the NIA and at what levels? What are the NIA's research priorities in the area of long term care?

Dr. Williams. The National Institute on Aging is currently supporting about $35 million of research on different aspects of long-term care (LTC) research, including: epidemiology and forecasting of LTC needs; prevention, rehabilitation of chronic diseases and disabilities requiring long-term care; diagnosis and assessment of such conditions; and patterns and consequences of informal and formal care.

NIA's research in LTC is laying the knowledge base for legislative, regulatory, professional and personal interventions to reduce the needs for LTC either at home or in institutions, improve the quality of life for older people needing LTC, diminish burdens on families, and decrease societal costs.

Specific research areas include:

o in-home and supportive services that foster independence of frail older people;

o family care, and community and work-site programs that reduce the burdens on family caregivers;

o effectiveness of different ways of organizing and delivering formal and informal health care services for older people;

o burdens of care for Alzheimer's disease, with specific attention to the assessment of special AD units ;

o forecasting the supply and demand for LTC;

o the economics of LTC;

o interventions to prevent and treat disabling conditions common in old age such as urinary incontinence, osteoporosis, Alzheimer's disease;

o reducing frailty/injuries and associated long-term care needs;

o biomedical and psychosocial aspects of rehabilitation; and

o continuing and expanding the longitudinal National Long Term Care Study that is currently the Nation's key survey on LTC.

Mr. Roybal. To what extent and how is the NIA focusing on the long term care needs of special populations, including the oldest old, older women, rural and central city elderly, and racial and ethnic elderly?

Dr. Williams. In all research solicitations NIA encourages research attention on the special LTC needs of the rapidly increasing numbers of the oldest old, and also of racial and ethnic minorities, low income, rural elderly, and mentally retarded older adults. Moreover, it is NIH grants and contracts' policy that all research applications include women and minorities in their study populations or specifically justify their exclusion. However, very little is known about the use of and access to long-term care services in such special populations.

As a consequence, NIA is planning a focused research initiative on minorities and long-term care. Special attention to long-term care needs of rural populations is being requested in the recently released exploratory center grant on the health and effective functioning of older rural populations. Forecasting the special LTC needs of the oldest old population and establishing the major risk factors for LTC is a major component of the oldest old initiative. The National Long Term Care Survey is the central element in this initiative. An important part of NIA's program on physical frailty and long-term care is a new FY 1991 initiative for research on special problems associated with frailty in minority groups. There is considerable interest from the research community on this important topic.

Mr. Roybal. What have we learned that may be helpful in the development of federal policy toward long term care?

Dr. Williams. I would like to highlight three kinds of findings:

Health professionals often inappropriately use age as a criterion for clinical decision making regarding prevention, treatment and rehabilitation. Not only do physicians and other health care providers treat older patients differently from younger ones, but their differences in style of relating to patients have important health consequences. We are beginning to understand how to design specially targeted physical and/or psychosocial interventions that can improve the functioning of older people and thus reduce the need for long-term care.

Families are under a tremendous strain in providing long-term care to their frail and disabled loved ones. The addition of public health services/social supports does not diminish families' willingness to provide care; such services often complement rather than substitute for family care. Studies shows that families actually increase the amount of care provided to loved ones as their disabilities increase, often at the expense of their own health. Federal policies need to recognize and support the substantial contribution made by families and friends.

Contrary to expectation, the introduction of formal supports and services often does not make a dramatic difference in use of institutional care. Previous research studies have often not considered critical factors such as population targeting, the appropriate timing of interventions, the intensity of interventions needed to achieve the desired effect, and the assessment of outcomes in terms of patient and caregiver well-being and quality of life. Attention to such issues in the future can improve our understanding of the effectiveness of different forms of long-term care.

PATIENT ASSESSMENT AND CASE MANAGEMENT

Mr. Roybal. In reference to patient assessment and case management tools for long term care, describe what has been learned from NIA's research initiatives?

Dr. Williams. Patient assessment tools are very valuable for identifying older people who need care and for assessing the outcomes of different kinds of treatments. Some NIA research has focused on the reliability and validity of different kinds of assessment tools. For example, with NIA funding a screening tool was developed to predict institutional placement and to classify nursing home residents with respect to functional, cognitive, and behavioral characteristics.

NIA supported investigators working on the National Long-Term Care Survey have developed measures of disability and need for long-term care that can be used for general long-term care planning. A recent publication by the Federal Forum for Aging Related Statistics reveals how different surveys and different methods of asking questions often result in widely varying estimates of long-term care needs. Additional research is clearly needed to produce greater comparability in such estimates.

While self-report instruments have been proven in NIA research to be excellent actuarial tools for planning, they may give only a general indication of the magnitude of chronic conditions or disabilities. Older people tend to over report conditions producing evident impairment and disability and to underreport "silent" or asymptomatic disease conditions. NIA supported researchers have developed more powerful multi-variate based measures of disability needing LTC assistance. Additionally, NIA is working with the National Center for Health Statistics to include performance based measures of functioning and disability that can be used to link medical risk factors to physical disability.

NIA is just embarking on a multi-center controlled evaluation of geriatric assessment units to determine their effectiveness in identifying patient problems and reducing overall health services utilization and cost. Additionally, a major part of Frailty and Injuries: Cooperative Studies of Intervention Techniques (FICSIT Trials) will be to develop standardized assessment protocols for evaluating the effectiveness of the interventions and for identifying those who are most likely to benefit from treatment. Our Alzheimer's Disease Research Centers and Registries have also

made substantial progress in identifying reliable and valid instruments for assessing cognitive abilities.

Mr. Roybal. From the research initiative funded and in your professional opinion, what would be the best patient assessment and case management tool to implement into a long term care plan?

Dr. Williams. We are not yet ready to select one best instrument. The NIA sponsored Consensus Development Conference on Geriatric Assessment Methods for Clinical Decision Making identified necessary steps, elements and professionals to be involved in conducting such assessments. Model comprehensive geriatric assessments include two essential components: targeting of persons most likely to benefit especially in the inpatient setting and linking assessment with follow-up procedures. We would like to stress the importance of separating out assessments for individual treatment and case management from determination of benefit eligibility.

Mr. Roybal. What future plans does NIA have for further research on the development of patient assessment and case management?

Dr. Williams. We will continue our support of patient assessment methodologies in terms of large scale survey research and clinical research. We are particularly interested in developing a easily administered tool that can be used for estimating and forecasting the needs for long-term care. With regards to case management, we are continuing our investigations of the effects coordination or lack of coordinated care on patient outcomes and health care use. We will be paying special attention to the role of in-home health and supportive services and these linkages to family care and formal medical care services.

SPECIAL OLDER POPULATIONS

Mr. Roybal. Please describe the current status and your future plans for research on special older populations, such as racial and ethnic minorities, older women, central city elderly, rural elderly, mentally retarded adults and the oldest old.

Dr. Williams. NIA has long recognized that older Americans are very diverse. They cannot be treated as alike for most research purposes. People disadvantaged by birth, circumstance, or very advanced age, need particular attention. Long-standing initiatives explore racial and ethnic differences through research on such topics as life expectancy, effective functioning and healthy aging, dementia, bone density, and vision and hearing. Future plans include adding minority older people to on-going studies of dementia, increased research on ethnic variations of informal, family care for minority elderly, and, if FY 1991 funds are available, a Request for Applications on specific studies of conditions responsible for physical frailty in older minority populations. The extensive body of knowledge on older women generated by NIA-supported research formed the basis of a recent new research initiative on the relations among gender, health and longevity in old age. A Request for Proposals to be issued by the

intramural Epidemiology, Demography and Biometry program will focus on the causes and course of disability in older women.

As a critical part of its research program on physical frailty, NIA has developed a new FY 1991 initiative for research on special problems associated with frailty in minority groups. There is considerable research interest in this important problems.

Another major effort underway to include special older populations in research and to conduct research to elucidate the nature of their unique social and biomedical situations is through the Alzheimer's Disease Research Centers program. A set of satellite diagnostic and management clinical sites will be established in FY 1990. The purpose will be provide access to minority, rural or other under served people to the clinical core services of the ADRCs. The satellite clinics will allow the ADRCs to diversity the characteristics of their research patient populations and will provide access to many groups to the services of the ADRCs. A major goal within the extramural epidemiology program has been the development of studies of the incidence, prevalence and risk factors for AD in Black and Spanish-speaking populations. An important component of this goal is the development of instruments that are culture, education, and linguistically un-biassed for use in population based studies.

In response to evidence of specific research needs, NIA has also recently developed initiatives on older adults who are retarded, and on aging rural populations. Centers on Rural Aging are being established to complement ongoing NIA intramural studies among urban and rural populations in East Boston, Iowa, New Haven, and Durham, North Carolina. The new rural initiative will provide useful comparison data for studies of inner city minority elderly currently supported by NIA.

The fastest growing age group, the oldest old, or 85 plus, is also the group with the highest risk for dependency. NIA issued two program announcements targeted to this group and is stimulating research on factors fostering continued health and functioning, and on forecasting life expectancy. Planning has begun for continuing vital databases, such as the National Long Term Care Survey, improving cause of death data, and developing social indicators such as active healthy life expectancy.

FRAILTY CLINICAL TRIAL

Mr. Roybal. You are planning a Frailty Clinical Trial in FY 1990 to test interventions to reduce physical frailty and its consequences in older persons? Will all promising interventions be tested?

Dr. Williams. In response to NIA's solicitation, 42 proposals to conduct clinical trials of interventions to reduce frailty, falls, and associated long term care needs were submitted. Twelve were very highly rated; however, budgetary limitations allow funding only eight sites. Interventions include leg strengthening, balance and flexibility training, other rehabilitation strategies, nutritional interventions, fall and hip fracture prevention

programs, and environmental/behavioral strategies. Very strong unfunded proposals deal with physical therapy upon hospital discharge, hospital and nursing home rehabilitation regimens, and a sophisticated and unique exercise rehabilitation program.

It is critical to note that the Frailty Clinical Trials will test only a segment, albeit a very important one, of potential interventions against frailty. Because of the huge scope of this problem, NIA has organized a comprehensive long range research program aimed at continuing reductions in frailty and the care burdens it imposes. Other components of NIA's frailty research program include:

o Geriatric Rehabilitation. Millions of frail older persons could be restored to greater independence by rehabilitation, but better techniques are needed, especially for the 200,000 hip fractures occurring each year in older persons. Besides its Frailty Clinical Trials initiative, NIA has solicited proposals for biomedical and psychosocial research needed to achieve the enormous potential of geriatric rehabilitation. In 1990, NIA will also address a serious need for researchers with combined expertise in rehabilitation and aging by introducing special research career awards in this area.

o Geriatric Assessment. A recent NIH Consensus Conference panel noted the value of geriatric assessment in improving health outcomes and reducing health costs, and recommended research to improve assessment strategies further. Such strategies are crucial for improved long term care eligibility and reimbursement policies, since they could identify persons with treatable or preventable disabilities, for whom proper treatment and services could reduce long term care needs. Several approaches are ready for testing.

o Frailty in Minorities. Genetic, psychosocial and environmental factors affect risks for disabling diseases and abilities to cope with frailty and its consequences. To develop effective strategies to reduce frailty and disability among minorities, we need to learn more about the effects of these factors in different groups.

o Improving Medication Use Among Frail Older Persons. Geriatric patients often take several drugs whose side effects worsen frailty by impairing balance, orientation, and daily activities. Congressional hearings have highlighted severe health problems and costs due to poor drug prescribing for older persons. NIA has issued a Request for Applications for research to provide solutions to this problem. About 100 applications are anticipated, at least 25 of very high quality.

o Urinary Incontinence (UI). UI afflicts five million older Americans, and causes over $10.3 billion per year in health care and related costs. UI is a serious cause of disability and long term care needs among frail older persons, afflicting half of nursing home residents. NIA's UI research program includes both biomedical and behavioral approaches and has produced significant advances in treatment, but only a fraction of the potential for improvement. A 1988 NIH Consensus Conference recommended a major research

initiative on UI. NIA's 1989 solicitation for proposals in response to these recommendations has engendered considerable interest.

o Fundamental Progress on Chronic Musculoskeletal Diseases and Disorders of Gait and Balance. Physical frailty would be dramatically reduced by better treatments for degenerative diseases which impair physical functioning among older persons. NIA has established a major osteoporosis program, focused particularly on preventing hip fractures. Clinical trials are now feasible in this area. Opportunities for progress against osteoarthritis, degenerative muscle conditions, and age-related disorders of gait and balance also merit increased research.

In summary, NIA has established a very active program on geriatric physical frailty which reflects a serious, long-term commitment to this critical area of inquiry. Progress in the above areas should lead to major reductions in dependence and long term care needs of older persons.

Mr. Roybal. What will the long run impact of these trials be?

Dr. Williams. As I noted at an October 1989 briefing requested by the U.S. Senate and House Committees on Aging, the Frailty Clinical Trials (FICSIT) can have a major impact on dependence and long term care needs. These interventions could significantly increase older persons' abilities to live independently, and prevent falls and disabling injuries such as hip fractures. Since physical frailty afflicts literally millions of older Americans, the potential public health benefits and reductions in long term care burdens are enormous. The studies will provide information for both community-dwelling and institutionalized older persons. Because the FICSIT trials will be looking at several critical outcomes such as functional status, mobility, general health, falls, and many others in a coordinated way, the findings can be expected to offer critically needed knowledge on ways to reduce dependency and improve the quality of life of older persons.

Mr. Roybal. What mechanisms will be used to disseminate the results of these trials?

Dr. Williams. The NIA's Public Information Office has begun actively publicizing the Frailty Clinical Trials, which have received the acronym FICSIT ("Frailty and Injuries: Cooperative Studies of Intervention Techniques"). Thus, we hope to increase public awareness of FICSIT over the course of the trials. We plan to disseminate results both to the public and professional groups through presentations to such groups as the American Public Health Association, American Geriatrics Society, American Nursing Association, American Academy of Rehabilitation Medicine, American Physical Therapy Association, and many others. Also, staff of other organizations such as the American Association of Retired Persons and the Alliance for Aging Research have indicated a desire to aid in dissemination of the trial's results.

Mr. Roybal. In your professional judgement, what would be an appropriate level of support for these studies?

Dr. Williams. My professional judgement is $5.5 million per year for three years will support adequately the Frailty Clinical Trials (FICSIT). This would allow funding the twelve best sites, each of which offers a unique contribution. Since $2.9 million will be awarded for limited funding of eight sites in FY 1990, an additional $2.6 million in FY 1991 would fully fund all twelve sites. This is part of a comprehensive NIA research program on frailty, which includes additional related areas listed above. Current support for these is approximately $25 million per year. Based on present research needs and opportunities, additional $28 million would provide appropriate support for such areas geriatric rehabilitation, geriatric assessment, frailty studies in minorities improved medication prescribing, urinary incontinence, and clinical trials of osteoporosis treatments.

PRODUCTIVITY IN WORK AND RETIREMENT

Mr. Roybal. Older people often spend several decades in retirement. What research is NIA doing or planning relevant to older people's productivity in work and retirement?

Dr. Williams. NIA's long-standing program on Productivity, Work, and Retirement addresses the fact that increasing numbers of able older people constitute an untapped and little understood national resource. This research has repeatedly demonstrated two broad principles: active participation in social roles can improve older people's productivity as well as their health, intellectual functioning, and independence; but older people's productivity is contingent upon the availability of roles that encourage and reward active participation, and that aid continuing practice of existing skills and learning of new ones.

Millions of disengaged older people could become more productive, through research to guide implementation of these broad scientific principles. Few productive roles are currently available. For those older people who do not want to retire, opportunities in the work force continue their secular decline: today less than half of men aged 55 and over are in the labor force, a fraction that could drop to only one-third by the year 2000. Similarly, for those frail older people who want to remain independent in the household, few supports are provided.

Two types of relevant research are included in the NIA Program on Productivity, Work, and Retirement. First, wide-ranging specific studies will lay the knowledge base for designing interventions to improve productivity in the workplace and the household and community. These studies aim to understand what kinds of roles and environments are needed and how they can influence older people's effective functioning and independence. Such studies are essential for testing hypotheses derived from large-scale cross-sectional or longitudinal studies, of which the Health and Retirement Survey is a prime example. Second, the Health and Retirement Survey will establish a cohort of people and track their health and financial status throughout the stages of pre-and post-retirement.

URINARY INCONTINENCE

Mr. Roybal. Could you tell us, Dr. Williams, what is the impact of urinary incontinence on the lives of our older citizens?

Dr. Williams. Urinary incontinence (UI), is particularly prevalent, morbid, and costly in older persons. At least five million older Americans, and approximately half of all nursing home residents, suffer from UI. It is estimated that the costs of this problem total $10.3 billion per year. Beyond the monetary costs, the toll in limitation of activity and constriction of social interactions of afflicted persons is very considerable. UI is frequently a contributing factor to nursing home admission.

Mr. Roybal. What research has the NIA done to improve our understanding of and treatment for urinary incontinence?

Dr. Williams. NIA has supported a program of research grants on UI since 1982, involving urologists, gynecologists, geriatricians, behavioral scientists, and nurses at numerous research sites. This research has included the first community-based epidemiologic study of UI in the U.S., and subsequent clinical trials demonstrating effective interventions to reduce UI in both community-dwelling persons and nursing home residents. Recent studies have revealed previously unknown causes of UI, pointing the way toward more effective treatments.

Mr. Roybal. What additional research needs to be conducted on urinary incontinence? What federal resources would be needed to conduct additional research?

Dr. Williams. Research to date has only addressed a small fraction of the potential for improved prevention and treatment of this problem. A 1988 NIH Consensus Development Conference on Urinary Incontinence recommended a major research initiative to improve assessment and treatment for UI, particularly:

- o basic research on the causes of UI;
- o epidemiologic studies of risk factors for UI in specific populations (particularly males and nonwhites), and the impact of UI on physical and mental health;
- o development of strategies to prevent urinary incontinence;
- o randomized clinical trials of specific behavioral, pharmacologic, and surgical treatments;
- o development of new therapies, including pharmacologic agents, new behavioral and surgical strategies, and other innovative techniques;
- o research on other common disorders of urinary dysfunction, including urgency, frequency and retention;
- o techniques to incorporate improved behavioral and other treatments for UI into standard health care; and

o psychosocial factors in UI management.

In response to these recommendations, NIA issued a program announcement in 1989, soliciting research on these topics. There is considerable interest in this area from the research community. This initiative would cost approximately $6 million per year above present levels for the next five years.

DISSEMINATION OF INFORMATION ON URINARY INCONTINENCE

Mr. Roybal. What mechanisms has the NIA utilized to disseminate information on urinary incontinence to the medical, nursing and caregiver's communities?

Dr. Williams. An NIH Consensus Development Conference entitled "Urinary Incontinence in Adults" was held October 3-5, 1988. This conference was sponsored by the National Institute on Aging and the Office of Medical Applications of Research of the National Institutes of Health, in conjunction with the National Institute of Diabetes and Digestive and Kidney Diseases, the National Center for Nursing Research, the National Institute of Neurological and Communicative Disorder and Stroke and the Veterans Administration.

The Consensus Development Conference provided an overview of current knowledge on the etiology, pathophysiology, sequelae, and management of this prevalent clinical problem. Although information on incontinence is increasing, the field has long been neglected, and numerous gaps exist in our knowledge. While many controversies were addressed, numerous questions were identified that await answers and thus serve as the focus for future research directions.

This conference was broadcast to hospitals across the country for education of health professionals, and a video tape of the conference is available for continuing education activities. A conference report was published in the Journal of the American Medical Association. Inquiries to the NIH for information about this topic and for copies of the Consensus Development Consensus Statement have been extraordinary in number.

OSTEOPOROSIS

Mr. Roybal. What is the impact of osteoporosis in older adults?

Dr. Williams. The impact of osteoporosis is most severe in advanced age, when it produces its greatest public health burdens. Osteoporosis is present in epidemic proportions among older adults, afflicting 90 percent of women over age 75, and large numbers of older men as well. Its most significant impact in older persons is mortality and disability from hip fractures. Of the more than 227,000 hip fractures that occur in the U.S. every year, almost 50 percent are suffered by persons 80 years of age or older. There is an alarming 12 to 20 percent mortality rate from hip fracture, and 20 percent of the survivors will be admitted to nursing homes, often

for the rest of their lives. In fact, 40 percent of nursing home admissions are related to falls.

Besides its burden of death and disability, osteoporosis among older persons imposes huge health costs. The annual cost of osteoporotic fractures is more than $10 billion, over $7 billion of which are due to hip fractures. Because hip fracture rates increase so sharply with age, delaying the onset of severe osteoporosis by only six years could reduce hip fracture-related costs by over $3.5 billion per year.

TREATMENT FOR OSTEOPOROSIS

Mr. Roybal. What are the potential treatments for osteoporosis in older adults?

Dr. Williams. While estrogen replacement therapy remains the most effective proven therapy for postmenopausal--estrogen dependent--osteoporosis, it does not significantly build bone mass, nor is it clear that treatment is effective beyond the first decade after menopause. It is also not a treatment for male osteoporosis which leads to high fracture rates in men over age 70.

Thus, we need to explore other promising interventions. These include exercise, dietary calcium--which preliminary evidence indicates may be much more effective than previously thought--vitamin D, thiazides--commonly prescribed diuretics which may also prevent bone loss--bone growth factors--both local and systemic--and calcitonin and other hormones which might lead to practical treatments of osteoporosis. One of the most significant outcomes demonstrated in NIA studies are the synergistic effects of combined interventions.

Mr. Roybal. Which treatments would reduce health burden?

Dr. Williams. Therapy that can significantly slow bone loss, especially loss of cortical bone in the hip, in older persons could markedly reduce osteoporotic fractures. Preliminary evidence indicates that two interventions may be especially cost-effective in achieving this goal:

Exercise. It has been well established that lack of mobility results in bone loss. Yet, among community-dwelling people over 65 years of age, only 42 percent walk for exercise at least twice a month and 72 percent take no form of exercise at all. In St. Louis, thirty-five postmenopausal women ranging in age from 55 to 70 were studied to assess the effect of weight bearing exercise training on bone mineral. After 22 months of exercise, bone mineral content had increased an average of 6.1 percent in the study participants. Further studies are needed to determine the amount of exercise needed to produce the greatest increases in bone density.

Exercise programs for older people can also strengthen muscles in both men and women of very advanced age, helping to decrease the risk of falls when morbidity and death from fractures are highest. For example, a group of nursing home residents--average age of 90

years--some even in wheel chairs, more than doubled their leg strength after an eight week course of weight lifting exercise.

Dietary Calcium. Calcium supplementation is safe, well tolerated, and relatively inexpensive compared to many other potential treatments for osteoporosis. If demonstrated to be effective and used by persons at risk for osteoporosis, the total cost of calcium supplementation would be less than five percent of the current costs of osteoporotic hip fractures alone. Though calcium supplements have not proved to be as efficacious as hoped in preventing bone loss in postmenopausal women--type I osteoporosis--a group of older patients with vertebral fractures treated with calcium supplements had a significant increase in bone mineral density over a four year period. Untreated women usually lose bone through age 75 and probably well into their eighties. A controlled study of the effectiveness of calcium supplementation in preventing fractures is thus greatly needed.

OSTEOPOROSIS FUNDING

Mr. Roybal. What is the award rate at the NIA with respect to osteoporosis?

Dr. Williams. In FY 1990, NIA expects to fund 6 of 30 approved osteoporosis research applications for an award rate of 20 percent.

Mr. Roybal. How much funding would be needed to expand the areas of research to 50% and 100%

Dr. Williams. In FY 1991, NIA would need approximately $7.0 million to fund 50 percent of approved osteoporosis applications. Approximately $12.8 million would be needed to fund 100 percent of approved applications. These figures include FY 1991 applications already received or expected, plus the backlog of unfunded approved FY 1990 applications which could be funded in FY 1991. These figures are are based simply on the current level of activity.

ADDITIONAL OSTEOPOROSIS RESEARCH

Mr. Roybal. Does additional research need to be conducted on osteoporosis?

Dr. Williams. Yes it does. Despite significant advances in osteoporosis research, none of the questions raised at the 1984 Osteoporosis Consensus Development Conference have been fully resolved. Much of the basic research on the mechanisms that cause osteoporosis remains to be done. More must be known about risk factors that can be modified. Promising treatments must be tested in population-based clinical trials. NIA's plans for initiatives in important research directions include:

Testing interventions in advanced age. Studies suggest that, even in old age, osteoporosis can be arrested or even reversed. However, we lack knowledge on treatments, such as estrogens, calcium, vitamin D, and physical exercise, in older persons, whose responses are likely to differ significantly from the middle-aged. Thus, we do not know whether the potentially great benefits of these

treatments for the 19 million Americans over age 70 outweigh their costs and side effects. Clinical trials can resolve these issues, and increase basic knowledge about progression of osteoporosis in old age, leading to still better prevention and treatment.

Aging and bone regulatory factors. Besides clinically used hormones such as estrogens, many circulating factors and substances in bone regulate its formation and breakdown. These factors, or drugs which affect them, could be more effective against osteoporosis than any current treatment. However, research on most of these is at an early stage. To develop safe, effective clinical uses, we need to know much more about how they work. We especially need to know the effects of aging processes, since levels of these factors, and responses to them, are altered in many aged persons. Without this knowledge, we may miss the chance to use these factors effectively for older persons, who may need them most. Though a small pool of well-trained researchers currently studies bone regulatory factors, many more are needed, particularly with combined expertise in aging.

Hip fracture rehabilitation. Preventing hip fractures by development of effective treatment for osteoporosis is the most fundamental approach to this problem, but until this is achieved, better rehabilitation techniques for osteoporotic hip fracture patients remain an important challenge. Rising interest in geriatric rehabilitation research makes this an especially opportune time for emphasis on this area.

Lifelong strategies against osteoporosis. Because risk of osteoporosis is determined by peak bone mass in adulthood as well as later loss, prevention strategies span the lifetime. Developing and testing such approaches involves issues such as childhood nutrition, exercise, estrogen replacement therapy, and nutritional needs of older persons. This effort potentially involves interests of several NIH Institutes, including NICHD, NIDDK, NIAMS, and NIA. A model of collaboration in this field is the ongoing PEPI (Postmenopausal Estrogen-Progestin Interventions) study, sponsored by NHLBI, NIDDK, NIAMS, and NIA, which measures effects on bone as well other endpoints. However, PEPI addresses only a few of the issues about lifelong prevention of osteoporosis, which would require more extensive efforts.

Mr. Roybal. Can you describe what general area of research the NIA is currently conducting?

Dr. Williams. The overriding research goal of the NIA Osteoporosis Program is better methods of preventing osteoporotic fractures of old age by slowing or stopping bone loss and bone fragility, identifying and reducing risk factors that cause falls and hip fractures in older people, and treating and rehabilitating fracture patients of advanced age. Thus, osteoporosis research is an extremely critical element in NIA's overall effort to develop ways to reduce physical frailty and dependence among older persons.

NIA's osteoporosis program has a special focus on aging-associated aspects of this disease. Because bone loss is almost universal with increasing age, NIA supports research to identify

age-associated processes responsible for osteoporosis and strategies based on modifying them. Such strategies offer the promise of fundamental major progress in preventing or curing this disease. NIA especially emphasizes osteoporosis in advanced age, when it is most severe and causes the most severe disability and mortality, especially from hip fractures. Because many aging processes are modifiable by exercise, nutrition, and other factors, NIA is placing an increasing emphasis on testing interventions against osteoporosis.

NIA's aging-oriented focus on osteoporosis research includes molecular- and cellular-level projects, bone density studies, clinical investigations of fractures, community-based studies of prevalence and risk factors associated with osteoporosis, investigations of the social and behavioral consequences of fractures, and clinical intervention trials. The major categories of research in the NIA osteoporosis program include:

o Characterizing the causes of bone loss in old age

o Modifying the factors that affect bone loss such as exercise, hormone replacement, nutritional factors--including calcium, fluoride, vitamin D, protein, phosphorus, and alcohol--and age-related changes in bone regulatory factors and bone-regulating hormones

o Lessening other risk factors for osteoporotic fractures such as falls, medications and environmental and other factors

In addition to supporting osteoporosis research its intramural and extramural programs, NIA is a partner in international osteoporosis research in the WHO Special Program for Research on Aging.

RESOURCES FOR FUNDING OSTEOPOROSIS RESEARCH

Mr. Roybal. What Federal resources would be needed to conduct such research?

Dr. Williams. Although we are already funding the highest quality and most important research in this area, there is always more that could be done. This would require an additional $13.8 million per year over the next five years over current support levels would be needed to realistically expand osteoporosis research.

OSTEOPOROSIS APPLICATIONS

Mr. Roybal. How many applications in the area of osteoporosis have been approved by the NIH study section?

Dr. Williams. NIH study sections have approved 30 osteoporosis applications eligible for funding in FY 1990. These include only applications assigned to NIA.

Mr. Roybal. How many applications have been funded?

Dr. Williams. Six of these applications have been funded in FY 1990. NIA supports an additional 31 ongoing osteoporosis projects begun in earlier years, and an additional 19 grants on osteoporotic fractures and risk factors for these fractures.

Mr. Roybal. How many applications are you unable to fund because of limited resources?

Dr. Williams. The NIA currently has 24 unfunded approved osteoporosis applications which will not be funded in FY 1990 due to limited resources.

Mr. Roybal. At the rate of current funding can you retain established scientists and attract new researchers to the field of osteoporosis?

Dr. Williams. The Federal Government must show a strong fiscal commitment to osteoporosis research and to training grants to attract new investigators to the field. Only new funds will make osteoporosis research attractive enough to draw competent researchers from other research fields to conduct necessary interdisciplinary research on osteoporosis. We must begin to consider developing public and private partnerships to help share the increasing budgetary osteoporosis research.

OSTEOPOROSIS COLLABORATION

Mr. Roybal. Can you describe the collaborative efforts among the NIH Institutes regarding osteoporosis?

Dr. Williams. There is appropriate overlap in osteoporosis research sponsored by the various NIH Institutes. Institute staff work closely to provide continuity in specific research areas and provide informal briefings on program priorities as they develop. Program Announcements and Requests for Applications are often co-sponsored by two or more Institutes, and projects are divided or shifted by mutual agreement to provide the grantees the best chance for funding, and to make the best match for program relevance. The NIA and sister Institutes jointly sponsor workshops, briefings, conferences, and publications in order to disseminate information about osteoporosis to the research and lay communities.

NIA collaborates with other Institutes and government agencies on interagency research projects, co-sponsoring conferences and producing osteoporosis prevention educational material for health professionals and the public.

OSTEOPOROSIS IMPACT ON LONG-TERM CARE

Mr. Roybal. What impact does osteoporosis have on long term care needs of older adults?

Dr. Williams. Osteoporosis is a major cause of long term care needs of older persons, primarily because of osteoporotic hip fractures. Older persons suffer more than 200,000 hip fractures per year. Of these, over one-fifth are unable to walk for at least one year following the fracture and many never regain the ability to

walk. Falls and associated injuries contribute to 40 percent of nursing home admissions and nursing home costs for hip fracture patients are over $4 billion per year. Fracture victims account for approximately nine percent of all disabled persons over age 85.

Mr. Roybal. What is the impact of osteoporosis in older adults on health care needs and costs?

Dr. Williams. In addition to the terrible toll of pain and suffering, osteoporosis causes a tremendous drain on health care resources. More than $10 billion per year is spent on osteoporotic fractures, 90 percent of which is for direct costs of treatment and care. About a fourth of all patients with limb fractures require hospitalization, and the mean hospital stay increases from 13.6 days among those age 25-44 to 32.6 days among those over age 65. Hip fractures, which are concentrated overwhelmingly in persons over age 65, account for more than half of all days of hospitalization for limb fractures. Hip fractures alone account for over $7 billion annually, costing approximately $30,000 per hip fracture.

Furthermore, because of the rapid increase in the oldest age groups, there will be 300,000 hip fractures per year by the year 2000, unless effective prevention and/or treatment is found. The cost of care for hip fracture in thirty years will increase from $7 billion to $30 billion per year, assuming that health care costs increase by only 3 percent per annum. Thus a cost-effective way of reducing hip fracture rates by half could save as much as $15 billion per year in future health costs.

OSTEOPOROSIS EDUCATION

Mr. Roybal. What is the NIA doing in reference to educating health professionals and the public about osteoporosis?

Dr. Williams. The NIA Information Office has utilized various forms of the media to educate health professionals and the public about osteoporosis:

- Issued press releases to publicize important research findings. Recently, the NIA issued a press release detailing the work of three grantees with new information as reported in JAMA. I also added an editorial in the same issue about osteoporosis.

- Wrote a fact sheet to be included in the packet of the National Osteoporosis Foundation (NOF) will distribute for National Osteoporosis Week.

- Distributed an Age Page fact sheet on Osteoporosis at National Conventions.

- I contribute a regular column for the NOF newsletter.

The NIA also sponsors conferences and workshops on osteoporosis. Most recently the NIA co-sponsored the second international conference, "Research Advances in Osteoporosis" which was held in Washington, D.C., February 26 to 28, 1990. In addition,

NIA and NIAMS staff co-sponsored a briefing on osteoporosis with Congressional staff during the Fourth Annual National Osteoporosis Week observance.

Mr. Roybal. Do you envision that there are opportunities to inform the public through a resource mechanism in the private sector?

Dr. Williams. The NIA Public Information Office works with staff and grantees to translate fruits of its research into information useful to public and private sectors. Every effort is made to utilize these networks and develop new ones.

An osteoporosis clearinghouse is another mechanism that could be used as a vehicle for public information. If specific funds were provided for this activity, government agencies such as the NIA could collaborate with a professional organization in the private sector who would be charged with the maintenance and administration of such a clearinghouse. The clearinghouse would receive, archive and distribute information from reliable research and educational sources on safe, efficacious and cost-effective ways to prevent and treat osteoporosis.

A clearinghouse initiative is especially timely since the public is faced with a bewildering amount of advice on health promotion and disease prevention topics. The area of osteoporosis is not exempt from this problem. In fact, osteoporosis may be especially hard hit by "information overload" because so many factors--calcium, fluoride, exercise, nutrition, and estrogen--are key to understanding it. A cooperative effort between the public and private sector is necessary before the public becomes unsure about what advice to follow. A clearinghouse serving as the central point for disseminating osteoporosis research results and general information to physicians and the lay public would be a first step toward solving this problem.

DISEASE PREVENTION

Mr. Roybal. Please describe any demonstration projects or research the NIA has conducted or planned which pilot preventive health services and disease prevention for older adults.

Dr. Williams. I would like to mention a few representative projects. NIA is currently supporting a national survey of self care practices which will identify preventive health services and disease prevention activities that older people with chronic diseases or disabilities utilize to help them live independently in the community. In the past we have also supported behavioral and environmental interventions to reduce urinary incontinence and to prevent falls. Moreover, in conjunction with the National Cancer Institute, we are currently supporting some social and behavioral interventions to increase older women's use of screening mammogram.

Mr. Roybal. What does this or other research tell us as to what health promotion and disease prevention strategies are most effective?

Dr. Williams. Contrary to popular assumptions that older people are not willing or able to change their behaviors, research is showing that: older people can be successfully recruited into health promotion programs; programs based on theories of behavioral change processes can indeed be effective in modifying individual behaviors and life-style practices; maintenance is often a problem, but older people are no less compliant to medical regimens than younger persons; and organizational strategies can be designed to reinforce individual behavior change. Research suggests that active participation by the older person is an important ingredient in successful outcomes as well as the design of interventions which are integrated into the older persons' normal care routines. Future initiatives focus on developing and testing psychosocial interventions in areas of specific concern to older people-- falls and injuries, breast cancer, harmful dietary practices.

THE OLDEST OLD

Mr. Roybal. The oldest old constitute the fastest growing segment of the elderly population. What is being done in the area of prevention to meet the potential needs of this age group?

Dr. Williams. The population over age 85, the oldest old, is indeed regarded by the Census Bureau to be the fastest growing age group in the nation. Moreover, a number of researchers have developed forecasts that dramatically exceed the Census Bureau's high range projections for the middle of next century. The Institute has in place an initiative on the Oldest Old that includes a focus on establishing the risk factors for functional decline and dependency as well as assessing the special needs of this unique group. Measures of active life expectancy, disability free expectancy, are being developed for use as indicators of effectiveness in this area.

For these objectives, longitudinal data are needed. To this end, the Institute has initiated and continued a number of the databases including the National Long Term Care Survey, the National Longitudinal Study on Aging, and The Established Populations for the Epidemiological Study of the Elderly. While many of the modifiable risk factors for disability at very advanced ages remain to be found, the Institute has begun, for example, clinical trials on falls and frailty that include the very old. However, since some risk factors for frailty, financial impoverishment, and institutionalization are likely to differ at advanced ages, epidemiological, demographic and economic studies are still needed. Some attention will be given to the robust oldest old since they might provide clues about factors that allowed them to maintain their health and vitality. Knowledge about modifiable risk factors is still too rudimentary in some areas to allow for the development of appropriate prevention and rehabilitation programs for the oldest old.

Mr. Roybal. What are the complexities in predicting the potential needs of this age group?

Dr. Williams. Predicting the potential needs of this age group requires reliable projections of the numbers of the oldest old and

their future health, social and economic characteristics. Since all those, except for immigrants, who will be aged 85 and over between now and the year 2075 are already residing in this country, the key variable for predicting the population size is future life expectancy. The Institute has funded a few studies that are attempting to develop these projections, including estimates of uncertainty. These models must be able to take into account the impact of health promotion and risk factor intervention programs on future life expectancy. One of these models has indeed forecast that healthier life styles, that is, reducing smoking, hypertension, cholesterol, etc., could plausibly result in some 40-60 million people over age 85 in year 2050 or 2060.

Some studies are also trying to develop forecasts of both morbidity and disability, known as active life expectancy, since the actual impact of this dramatic demographic change will be modified by the extent to which active, or healthy, life expectancy increases proportionately with disabled life expectancy. An important element in developing these predictions is the knowledge of how future cohorts entering this special age group will differ in having higher education levels or better or worse health from the current oldest old. Another complication is how all the myriad of factors are combined and interact, and the Institute is planning to include in the Oldest Old initiative the development of micro-simulation models. These models will help identify the implications of the dramatic growth of this population for the country's health system and costs, and also evaluate the impact of alternative changes. Finally, these efforts depend upon having appropriate data available. While the data on the oldest old have been improving, considerable further development is required since most surveys either exclude this age group or include too few for adequate analysis.

BEHAVIORAL AND SOCIAL ASPECTS OF AGING

Mr. Roybal. What initiatives are currently being undertaken by the NIA in the area of prevention to address the behavioral and social aspects of aging such as work and retirement, cognitive functioning, health and long term care?

Dr. Williams. NIA's long-standing program on Productivity, Work, and Retirement addresses the fact that increasing numbers of able older people constitute an untapped and little understood national resource. This research has repeatedly demonstrated two broad principles: active participation in social roles can improve older people's productivity, and their health, intellectual functioning, and independence; but older people's productivity is contingent upon the availability of roles that encourage and reward active participation, and that aid continuing practice of existing skills and learning of new ones.

Millions of disengaged older people could become more productive, through research to guide implementation of these broad scientific principles. Few productive roles are currently available. For those older people who do not want to retire, opportunities in the work force continue their secular decline: today less than half of men aged 55 and over are in the labor

force, a fraction that could drop to only one-third by the year 2000. Similarly, for those frail older people who want to remain independent in the household, few supports are provided.

NIA's plans include further research to guide interventions that can improve older people's opportunities for productivity and independence in two domains: in the workplace, many older people want and are capable of continuing some form of productive activity, either paid or unpaid; and in the household and community, many older people, especially those who live alone, want to function independently but have serious difficulty in securing assistance or in performing everyday tasks.

In the area of cognitive functioning, the National Institute on Aging is supporting research projects that attempt to link specific cognitive changes that occur during aging with their underlying brain chemistry and physiology. Advances in brain imaging techniques such as PET and SPECT scanning, which allow investigators to measure metabolic and chemical events in the brain non-invasively while people attempt to learn and remember different types of information, have made it possible to bridge gaps in our understanding of brain/behavior relationships. With this new knowledge about the underlying neural mechanisms and processes involved in cognition, it should be possible to develop more effective prevention and intervention strategies. In addition, the NIA is investigating the effects of various toxicants on cognitive functioning. By identifying environmental poisons, specifying their mode of action on brain functions, and then substituting less toxic alternatives, it should be possible to prevent or slow the progression of various neurological and degenerative diseases.

NIA has a major research solicitation on aging and health care which calls for social and behavioral research on the organization of health care services; provider-patient interactions and social and behavioral aspects of institutional care. Two recently funded health services clinical trials illustrate examples of prevention research in this area, one dealing with psychosocial interventions for reducing the use of passive restraints in nursing homes and the other with the effectiveness of different models of health care delivery for diagnosing and treating older patients.

One new initiative is being planned on factors affecting patients' motivation for and compliance with prescribed regimens and strategies for increasing health-promoting attitudes and behaviors. Additionally, the new Health and Retirement Survey will provide valuable information that will be used to develop programs designed to allow older workers who so wish to remain in the labor force longer than they are currently able.

Mr. Roybal. What level of funding is currently expended and what level is needed to support such initiatives?

Dr. Williams. These amounts are as follows (in millions of dollars):

	Current	Needed
Work and Retirement	$1.0	$ 3.0
Cognitive Functioning	$7.5	$12.0
Long-Term Care	$3.0	$10.0

PSYCHOLOGICAL IMPAIRMENT

Mr. Roybal. Please describe the NIA's programs of research to investigate behavioral and social aspects of elderly psychological impairment, including stress, on families and caregivers of psychologically impaired elderly persons.

Dr. Williams. The NIA's research emphasis in this area is upon the burdens of care associated with Alzheimer's disease. Caregivers of Alzheimer's patients often face overwhelming burdens. There is an urgent need for additional social and behavioral research on the nature and impact of caregiving burdens; the type of assistance currently being provided to caregivers; and the effectiveness of interventions for reducing these burdens.

NIA's initiatives to investigate behavioral aspects of psychological impairment in aging include major efforts to elucidate the neurological and psychological bases for such impairment. Some research currently supported by the NIA has shown that for many older adults psychological functions can remain stable well into the eighth decade. This would imply that signs of psychological impairment may not be a necessary concomitant of the aging process but rather may be indicative of disease states that may be remediable now or in the future. In order to stimulate research on these topics, NIA staff have developed the following Program Announcements: Age, Hearing and Speech Comprehension; Age and Visual Perception; and Cognitive Functioning and Aging. This coming fall, NIA will convene a conference, "Cognitive Neuroscience Approaches to Aging," to further develop research in this area.

Other examples of research topics include the impact of AD on different family members--what special problems do aged and frail spouses face?; strategies that caregivers are currently using to manage their own self care while caring for family members; caregivers' use of formal health care and the effect of public and private long-term care policies; psychosocial interventions for helping caregivers deal with disruptive behaviors; the effectiveness of community-based health and social services for AD patients and their caregivers such as respite care, board and care; the nature and effectiveness of specialized AD units for increasing patient functioning and reducing burdens of care; and forecasts of the magnitude of the disease and associated disability, the availability of support, and need for long-term care.

MENTAL HEALTH PROBLEMS OF THE ELDERLY

Mr. Roybal. Given the special problems facing nursing home residents with mental health problems, what NIA research has been conducted on the status of those residents and on what intervention and care strategies are most effective?

Dr.Williams. NIA supported research is documenting the extent of mental morbidity present in nursing home residents, which is much more than previously recognized. Findings from previous research stress the health and functioning benefits of increasing residents' sense of control over their environment to the extent possible given their cognitive and physical impairments. Specific intervention trials have demonstrated the effectiveness of behavioral strategies for reducing incontinence and the beneficial effects on patient and staff well-being. Newly funded research studies are examining the extent of behavioral problems in nursing homes and the effectiveness of reduced use of physical restraints or establishment of special care units.

MENTAL HEALTH TRAINING

Mr. Roybal. Please outline the activities which have been carried out through NIA training mechanisms?

Dr. Williams. From awards made in FY 1989, the NIA is supporting 12 institutional training and 5 individual career development awards related to psychological well-being and aging. These awards provide both pre- and post-doctoral training in the social and behavioral sciences and, in most instances, prepare researchers to be part of multidisciplinary research teams.

Mr. Roybal. How many training awards were funded in FY 1990 and how many are planned for FY 1991?

Dr. Williams. In FY 1990, the National Institute on Aging awarded 102 training grants to support 385 training positions and 91 career development awards. For FY 1991, we plan to award 92 training grants to support 385 training positions and 92 career development awards.

Mr. Roybal. How many of these awards were related to elderly mental health?

Dr. Williams. In FY 1990, eight institutional awards and three career awards will be funded that related to elderly mental health or psychological well-being. The same numbers also apply to FY 1991.

Mr. Roybal. What level of funding would be necessary to meet the training needs related to elderly mental health?

Dr. Williams. In order to meet the training needs in the area of psychological well-being and aging, the NIA would need an additional $1.5 million.

COORDINATION OF ELDERLY MENTAL HEALTH RESEARCH

Mr. Roybal. What steps have been taken to ensure coordination of the NIA's scientific activities related to elderly mental health with other NIH Institutes and with other governmental agencies which are doing related research, such as NIMH, AOA, and the Veterans Administration?

Dr. Williams. The NIA has extensive and frequent contacts with other NIH Institutes and governmental agencies through the Interagency Coordinating Committee for Research on Aging which the NIA chairs. Information and plans for various initiatives are shared and coordinated. More concretely, the NIA has issued program announcements and requests for applications as well as organized workshops and conferences in conjunction with other NIH Institutes and other agencies, such as the National Institute of Mental Health and the Administration on Aging.

ELDER ABUSE

Mr. Roybal. In the coming months, my Subcommittee on Health and Long-Term Care will hold hearings to examine the decade that has passed since the first Congressional hearings on elder abuse. Regrettably, I feel that we will reveal that the incidence of elder abuse--physical, financial, and psychological--is increasing and almost no Federal action has been taken to stem the tide. Has the NIA looked into elder abuse at all--how to prevent, detect, and treat it and who is the most likely victim and abuser?

Dr. Williams. The sensitive nature of maltreatment of older people makes research on the extent of elder abuse difficult. One NIA supported study, through telephone surveys of a random sample of elderly in Boston, found physical abuse, chronic verbal aggression and neglect reported by 32 elderly persons per thousand or a possible 700,000 to one million abused and neglected older people nationwide. Contrary to some popular notions, the highest proportion of abuse was between spouses, perhaps reflecting the high percentage of spouses who are caretakers for older people. The risk of abuse for elderly men was double that for women, again possibly related to stress of caretaking. Causes of elder abuse are poorly understood. However, the growing body of research on the burdens of caregiving suggest that continued stress may contribute to aggressive acts. More positively, this research is exploring approaches to alleviate such stress and thus holds promise for also reducing related elder abuse. More research is clearly needed to identify family units and older people particularly at risk of elder abuse, to educate older people who may be victims, and to develop ways to prevent and treat both the victims and abusers.

GUARDIANSHIP ARRANGEMENTS

Mr. Roybal. It is estimated that on any given day, over 500,000 Americans, most of them elderly, are under guardianship because they have been declared incompetent. Our Subcommittee has learned that many of these allegedly incompetent people are not incompetent, and that the diagnosis of incompetence has been made inappropriately. For example, in some states "old age" alone is sufficient cause for a person to be judged incompetent. Obviously, "old age" should not be the sole determinant of an individual's competence? Is it fair to say there are measures of competence? If not, is this a direction the NIA should take in order to prevent the inappropriate establishment of guardianship arrangements for the elderly?

Dr. Williams. There is no scientific or clinical justification for making the diagnosis of "incompetency" based solely upon age. A person's "competency" or ability to function ought to be based upon an assessment of cognitive capabilities. That assessment can only be performed using instruments that have been properly validated with age-appropriate populations according to strict scientific criteria. At present, there is no single standardized measure of competency. Current techniques for assessing sensory, cognitive, motor and behavioral capacities in the clinic are often inadequate and can lead to incorrect or inappropriate diagnoses. Sadly, too, there may be remediable conditions masquerading as dementias that are missed because current instruments are insensitive to the effects of nutritional, medical, or pharmacological status on normal cognitive functioning.

In response to the need for better assessment instruments and in order to prevent the inappropriate guardianship arrangements, the National Institute on Aging is making a major effort to improve assessment technology. In January 1990, an international workshop was convened, entitled "Neuropsychological Assessment Techniques for Use in Clinical Drug Trials of Alzheimer's Disease." Proceedings, including recommendations from a panel of expert neuropsychologists and behavioral neurologists, will be published later this year. Program announcements have been developed by the NIA to stimulate new research on instruments for measuring cognitive and sensory changes across the adult lifespan in both healthy and patient populations. Studies sponsored by the NIA using accurate and reliable measures of cognition are already yielding important results, including the finding that for many older adults, some cognitive capacities remain stable or may even show improvement through the eighth decade of life.

DISASTERS

Mr. Roybal. Natural emergencies, such as Hurricane Hugo and the San Francisco earthquake, do not discriminate on the basis of age -- persons young and old feel the effects of their devastation. Has the NIA done any research on the special needs of the elderly in the face of natural disasters -- like their frequent lack of mobility to escape the sites of impending disaster (such as Hugo, the course of which could be predicted fairly accurately), their centers afterwards, the difficulty they might have filling out forms for relief, etc. Has the NIA tackled this problem in any meaningful way?

Dr. Williams. The NIA has not supported any research directly on older people and natural disasters, although much of NIA's basic research on cognitive functioning and coping with stress is relevant to this topic. Disaster research is particularly hard to conduct because of the need to place investigators quickly into the field. The NIA does not have a suitable funding mechanism that allows the quick processing and review of an research grant application.

SAFER HOUSING FACILITIES

Mr. Roybal. Another type of disaster which occurs all too frequently is fires in institutions housing the elderly. Just

Tuesday, we heard reports of a nursing home fire which killed three people in Arkansas. Has the NIA done any studies to show what's needed to make facilities housing the elderly safer? If not, isn't this a worthy project?

Dr. Williams. Older adults are at serious risk from residential fires. Death rates from fires and burns in the older population are substantially higher than for younger age groups. It is of particular concern that many smoke alarm systems are inappropriately designed to match the sensory and motor capabilities of older adults. NIA activities that contribute towards making housing safer can be separated into those projects that seek to prevent accidents by researching ways to make housing more suited to the capacities of older adults, and those that seek to reduce the consequences of accidents by, for example, allowing swifter escape in case a fire does occur.

Prevention-related studies include research assessing how kitchen and other home environments can be improved to reduce demands on reaching such as over a stove top to a high cupboard and, as part of a comprehensive falls prevention/ health promotion study, research on an assessment tool for estimating environmental hazards. Special attention to fire hazards could be added to this investigation. Studies on reducing the consequences of accidents include preliminary work on producing a smoke and fire alarm system that is especially suited to the capabilities of older adults.

PREVENTIVE MEDICINE

Mr. Roybal. With my colleagues, Congressman Ralph Regula and others, I have recently introduced legislation to provide Federal funding for such preventive services as cancer screening and immunizations. What is the view of the NIA as to the importance of preventive medicine, a facet of health care which our Federal health care programs such as Medicare have so long ignored?

Dr. Williams. I believe preventive medicine is especially important for older Americans. Much of NIA's clinical research focuses on improving techniques for preventing disease and disability. One example is the set of Frailty Clinical Trials (FICSIT) which will test the benefits of techniques to prevent physical disabilities among frail older persons. NIA also supports research aimed at increasing the participation of older women in breast cancer screening programs.

I believe also that comprehensive geriatric assessment can play a critical role in prevention of disease and disability among older persons. Numerous studies have shown its efficacy in specific clinical settings. but if assessment is not targeted to those who will benefit, it may not be used effectively. There is a great need for studies to develop techniques of targeting appropriate geriatric assessment to those with preventible conditions and disabilities who would benefit.

FRAILTY CLINICAL TRIALS

Mr. Stokes. The NIA and the National Center for Nursing Research are collaborating to support clinical trials on interventions to reduce frailty and injuries in older people. What are the specific goals of this program?

Dr. Williams. These Frailty Clinical Trials, collectively known as FICSIT ("Frailty and Injuries: Cooperative Studies of Intervention Techniques") have the goals of reducing dependence, injuries and long term care needs by reducing physical frailty, that is, severely impaired strength, mobility, balance, and endurance, and falls. Interventions to be tested include leg strengthening, balance and flexibility training, other rehabilitation strategies, nutritional interventions, fall and hip fracture prevention programs, and environmental/ behavioral strategies.

The Frailty Clinical Trials (FICSIT) will test only a segment, albeit a very important one, of potential interventions against frailty. Because of the huge scope of this problem, NIA has organized a comprehensive long range research program aimed at continuing reductions in frailty and the care burdens it imposes. Other components of NIA's frailty research program include:

o Geriatric Rehabilitation. Millions of frail older persons could be restored to greater independence by rehabilitation, but better techniques are needed, especially for the 200,000 hip fractures occurring each year in older persons. Besides its Frailty Clinical Trials initiative, NIA has solicited proposals for biomedical and psychosocial research needed to achieve the enormous potential of geriatric rehabilitation. In 1990, NIA will also address a serious need for researchers with combined expertise in rehabilitation and aging by introducing special research career awards in this area.

o Geriatric Assessment. A recent NIH Consensus Conference panel noted the value of geriatric assessment in improving health outcomes and reducing health costs, and recommended research to improve assessment strategies further. Such strategies are crucial for improved long term care eligibility and reimbursement policies, since they could identify persons with treatable or preventable disabilities, for whom proper treatment and services could reduce long term care needs. Several approaches are ready for testing.

o Frailty in Minorities. Genetic and environmental factors affect risks for disabling diseases and abilities to cope with frailty and its consequences. To develop effective strategies to reduce frailty and disability among minorities, we need to learn more about the effects of these factors in different groups.

o Improving Medication Use Among Frail Older Persons. Geriatric patients often take several drugs whose side effects worsen frailty by impairing balance, orientation, and daily activities. Congressional hearings have highlighted severe health problems and costs due to poor drug prescribing for older persons. NIA has solicited proposals for research to provide solutions to this

problem. About 100 applications were received, at least 25 of very high quality.

o Urinary Incontinence (UI). UI afflicts five million older Americans, and causes over $10.3 billion per year in health care and related costs. UI is a serious cause of disability and long term care needs among frail older persons, afflicting half of nursing home residents. NIA's UI research program involves urologists, gynecologists, geriatricians, behavioral scientists, and nurses at numerous sites. This research has produced significant advances in treatment, but only a fraction of the potential for improvement. A 1988 NIH Consensus Conference on Urinary Incontinence recommended a major research initiative on UI. NIA's 1989 solicitation for research proposals in response to these recommendations has engendered considerable interest from the research community.

o Fundamental Progress on Chronic Musculoskeletal Diseases and Disorders of Gait and Balance. Physical frailty would be dramatically reduced by better treatments for degenerative diseases which impair physical functioning among older persons. NIA has established a major osteoporosis program, focused particularly on preventing hip fractures. Clinical trials are now feasible in this area, requiring approximately $6 million per year above current osteoporosis research support levels. Promising opportunities for progress against osteoarthritis, degenerative muscle conditions, and age-related disorders of gait and balance also merit increased research.

In summary, NIA has established a very active program on geriatric physical frailty which reflects a serious, long-term commitment to this critical area of inquiry. Progress in the above areas should lead to major reductions in dependence and long term care needs of older persons.

Mr. Stokes. What effect will the findings from these trials have on reducing dependency and improving the overall quality of life for older people?

Dr. Williams. As I noted at an October 1989 briefing requested by the U.S. Senate and House Committees on Aging, the Frailty Clinical Trials (FICSIT) can have a major impact on dependence and long term care needs. These interventions could significantly increase older persons' abilities to live independently, and prevent falls and disabling injuries such as hip fractures. Since physical frailty afflicts literally millions of older Americans, the potential public health benefits and reductions in long term care burdens are enormous. The studies will provide information for both community-dwelling and institutionalized older persons. Because the FICSIT trials will look at several critical outcomes such as functional status, mobility, general health, falls, and many others in a coordinated way, the findings can be expected to offer critically needed knowledge on ways to reduce dependency and improve the quality of life of older persons.

Mr. Stokes. What resources are needed to adequately support these trials?

Dr. Williams: In my professional judgement, $5.5 million per year for three years will support adequately the Frailty Clinical Trials. Research proposals to conduct these trials were submitted by 42 teams. Of these, 12 were very highly rated; however, budgetary limitations will allow the partial funding of only eight sites. Very promising but unfunded proposals deal with physical therapy regimens for older persons upon discharge from the hospital, development of hospital and nursing home rehabilitation regimens for persons 75 years and older showing recent losses in mobility, and a sophisticated and unique exercise rehabilitation program tailored for older persons. Since $2.9 million will be awarded for limited funding of eight sites in FY 1990, an additional $2.6 million in FY 1991 would fully fund all twelve sites. This is part of a comprehensive NIA research program on frailty, which includes additional related areas listed above. Current support for these is approximately $25 million per year. Based on present research needs and opportunities, additional $28 million would provide appropriate support for such areas as geriatric rehabilitation, geriatric assessment, frailty studies in minorities, improved medication prescribing, urinary incontinence, and clinical trials of osteoporosis treatments.

GERIATRIC REHABILITATION

Mr. Stokes. Many older people suffer from a variety of disabilities which could be lessened through rehabilitation programs. What research is the NIA supporting in the area of geriatric rehabilitation?

Dr. Williams. Literally millions of older persons suffer from physical and other disabilities which could be lessened by rehabilitation techniques. The interface between geriatrics and rehabilitation is so necessary that the modest development of geriatric rehabilitation to date is surprising. To promote progress in this much-needed field, the National Institute on Aging (NIA) places a major emphasis on rehabilitation-related research. NIA's current support for research in this area is approximately $10.8 million per year.

Needs and potential for rehabilitation among older persons are major foci of NIA's epidemiologic, behavioral, clinical, and basic research programs. NIA's epidemiologic studies are revealing the extent of specific disabilities in community dwelling populations, and identifying preventable risk factors for them. NIA's behavioral research programs are identifying behavioral and social factors which crucially affect older persons' responses to rehabilitation.

NIA supports clinical research on such topics as rehabilitation of disabling physical performance deficits in frail older persons and improved techniques of functional assessment for geriatric patients. Such studies have shown that even very frail older persons can show significant functional improvement in response to rehabilitation programs. NIA also supports research on cognitive rehabilitation techniques to counter age-associated memory problems. Basic studies on the causes of chronic degenerative conditions of later life, that may provide the basis for fundamental advances in rehabilitation strategies, are also an important NIA focus.

Three NIA initiatives of particular note in geriatric rehabilitation are:

Frailty and Injuries: Cooperative Studies of Intervention Techniques (FICSIT). NIA, in collaboration with the National Center for Nursing Research, has allocated $2.9 million per year, beginning in April 1990, to eight research teams to conduct clinical trials of improved interventions to reduce physical frailty and injuries in older persons. These trials will test rehabilitation programs to restore functional deficits related to cardiovascular, musculoskeletal, and other dysfunctions, and behavioral and environmental rehabilitation approaches to reduce dependency and risk of falls and injuries. The teams include researchers in physical medicine and rehabilitation, physical therapy, geriatrics, and related fields.

Program Announcement on Rehabilitation and Aging; Biomedical and Psychosocial Perspectives. This ongoing program is described in detail in the May 5, 1989 issue of the NIH Guide to Grants and Contracts. It encourages research grant proposals on rehabilitation for older persons with physical, sensory, and cognitive disabilities resulting from disuse, disorders, or injuries of the musculoskeletal, cardiovascular or other physiological systems. Research is encouraged on biomedical, social and behavioral aspects of rehabilitation and the combined application of medical and psychosocial strategies. This announcement covers rehabilitation of both newly developed and long-established disabilities in older persons.

Special Emphasis Research Career Award in Rehabilitation and Aging. Many experts in rehabilitation have noted that more persons trained in rehabilitation research are needed for this field to develop its full potential. This need is especially critical in rehabilitation and aging. To address this, in early 1990 NIA will introduce a program of Special Emphasis Research Career Awards to provide persons holding doctoral degrees in fields relevant to rehabilitation and/or aging with five years of career development support to acquire combined research expertise in these two fields.

Mr. Stokes. What are your plans for the future?

Dr. Williams. The FICSIT trials will identify which rehabilitation techniques show the most promise in retarding/reversing geriatric physical frailty, as well as identifying areas for further development of techniques is needed. NIA plans to support the development of such techniques in areas such as hip fracture rehabilitation, cardiac rehabilitation, and improved assessment techniques to identify older disabled persons who would benefit from rehabilitation. NIA plans continues emphasis on research career development in geriatric rehabilitation to remedy the shortage of trained researchers in this critical field.

LONG-TERM CARE

Mr. Stokes. I understand that you have a major initiative in the area of aging and long term care. Please tell us about this initiative.

Dr. Williams. NIA's research in long-term care (LTC) will lay the knowledge base for legislative, regulatory, professional and personal interventions to reduce needs for LTC and institutionalization, improve the quality of life for older people needing LTC, diminish burdens on families, and decrease societal costs. The program emphasizes the special LTC needs of racial and ethnic minorities, the oldest old, and the rural elderly. It plans to:

o Investigate frailty, osteoporosis, urinary incontinence, and other chronic illnesses and disabling conditions as a basis for prevention, treatment, and rehabilitation.

o Examine family care, linkages between formal and informal care, and work-site programs for helping employed caregivers.

o Assess in-home health and supportive services as a means of fostering independence of frail older people.

o Enhance the quality and efficiency of LTC by understanding the structure, processes and outcomes of care.

o Monitor and forecast the changing demand and supply of LTC.

o Develop, maintain and enhance national databases such as the National Long Term Care Survey that are key to research and the nation's planning and policy development.

o Understand the economics of LTC as experienced by older people, with special attention to feasibility of LTC insurance.

This initiative comprises several related NIA extramural and intramural programs priorities including reducing frailty and injuries, the burdens of caring for Alzheimer's disease patients, family support and care for older persons, and minority aging. The NIA is developing an implementation plan to coordinate the various aspects of this initiative and establish guidelines for stimulating research and training.

AIDS IN THE OLDER POPULATION

Mr. Stokes. Your justification states that approximately 10% of AIDS cases have occurred among those aged fifty or more, and that you expect this proportion to rise. Please tell us about your AIDS research program.

Dr. Williams. Two 1989 NIA program announcements addressed the fact that the older population is particularly vulnerable to HIV infection because of age-related decreases in the functioning of the immune system, blood transfusions received before 1985, and a lack of awareness of being at risk. These program announcements concerned: "Research on Behavior Change and Prevention Strategies to Reduce Transmission of HIV" and "Impact on AIDS of Aging and Changes in Immune Functioning." Future NIA program announcements, assuming AIDS funding is available, will deal with older people's awareness of and knowledge about AIDS and with the impact of AIDS on older people as both receivers and givers of health care. Research

is also needed on the effects on long-term care of older people exerted by the competing demands of the AIDS epidemic; on the adjustments of families when their adult children come back home because of terminal illness with AIDS; and on adaptations of sophisticated forecasting models to improve current estimates of future health care needs.

NIA is also cooperating with National Institute of Child Health and Development and other agencies on the cross-section survey of sexual practices and attitudes, with special attention to AIDS; and with the Agency for International Development and other components of NIH in a 1990 RFA on "Behavioral Research in Support of AIDS Prevention" in developing countries.

The Institute is also engaged in extensive intramural research in relation to functioning of the immune system in later life. Ninety individuals have been screened for an HIV vaccine trial, and tests on the immune function of individuals admitted to the trial are proceeding. An investigation of the effects of drugs on immune function has been expanded to study multiple exposure to amyl nitrate and THC. The Interleukin-2 receptor in serum from individuals undergoing AZT therapy provides a measure of the extent of the inflammatory process. These investigations into the mechanisms of age-associated immunodeficiency will result in the development of therapeutic strategies for its prevention.

WORKING GROUP ON MINORITY AGING

Mr. Stokes. The Institute now has a work group on minority aging. Who is on this work group and what is its mission?

Dr. Williams. The NIA established a Work Group on Minority Aging approximately a year ago which has as members the Associate Directors of each of the three extramural program areas: biomedical and clinical research, neurosciences and neuropsychology, and behavioral sciences research; the Associate Director of the Office of Planning Analysis and Communications; and the Deputy Associate Director of the Office of Extramural Affairs. The chairperson of the Work Group is the Assistant Director for Special Programs.

The Work Group is charged with the responsibility to develop plans for increased attention to research on issues of minority aging, improvement in quality of such research and increased involvement of minority investigators in research on aging. Assisting in implementation of plans and monitoring of progress towards established goals is also a responsibility of the Work Group.

In addition, the NIA-staff group works closely with the National Advisory Council on Aging's Task Force on Minority Aging which serves as a continuing advisory body to the NIA Director on minority issues overall including identification of priority research and training areas, and mechanisms of support.

OLDER PILOTS AND DRIVERS

Mr. Stokes. I am interested in research concerning continued competence in older pilots and drivers. How much are you doing in this area and how are you collaborating with other agencies?

Dr. Williams. Though issues of competency are involved in both piloting and driving, the different populations and circumstances involved in the two activities require that they be treated separately.

Accident patterns of pilots as a function of increasing age have yielded incomplete information on their safety in flight. NIA is seeking to supplement such data with studies of performance that examine how the expertise of older pilots interacts with any age-related changes in cognition and perception. Current studies are attempting to extend to piloting the general finding that expertise in a task diminishes or eliminates age differences. In addition, if funds permit, a Request for Applications will be released in FY 1991 calling for research on the flight performance of experienced older pilots. Preliminary contacts with staff in the Federal Aviation Administration and in the National Aeronautic and Space Administration are indicating areas of mutual interest.

In response to a Transportation Research Board study on Transportation in an Aging Society, NIA is working with a number of other federal agencies toward a coordinated federal policy on the research needed to improve the safety and mobility of older people. The tremendous predominance of driving as the preferred mode of transportation has ensured that the largest research effort is concentrated on this activity. NIA cosponsored a major workshop on driving needs together with the National Highway Traffic Safety Administration, the Federal Highway Administration and the Centers for Disease Control. Also with the National Highway Traffic Safety Administration, NIA is using data from established populations in Iowa and New Haven to construct a comprehensive model of driving behavior in older adults.

A major gap in the driving literature is the lack of any performance tests that reliably predict safe or risky driving in older adults. NIA is addressing this gap by supporting basic research on how the ability to do two tasks at the same time is related to aspects of driving difficulty, and by supporting longitudinal research on drivers with Alzheimer's disease to determine predictors of driving competence in this group.

COMPETING RESEARCH PROJECT GRANTS

Mr. Early. How many new and competing research project grants will you fund in FY 1991, and how does this compare to FY 1990 and FY 1989?

Dr. Williams. In FY 1991, the National Institute on Aging plans to award 153 competing research project grants. This compares to 156 awarded in FY 1990 and 194 awarded in FY 1989.

Mr. Early. What will the payline percentile be, and how does this compare to FY 1990 and FY 1991?

Dr. Williams. The National Institute on Aging awarded its competing research project grants to the 29th percentile in FY 1989. It is anticipated that the percentile will be 23 in FY 1990 and 21 in FY 1991.

Mr. Early. Can you give us some idea of what priority score this equates to?

Dr. Williams. In FY 1989, this would equate to a priority score of approximately 200 whereas in FY 1990 it would equate to 170 and to 160 in FY 1991. It should be noted that these are very rough estimates since there is no data available for comparison.

Mr. Early. What is the projected award rate for FY 1991?

Dr. Williams. The projected award rate for competing research project grants will be 17 percent in FY 1991.

Mr. Early. What about FY 1990 and FY 1989?

Dr. Williams. In FY 1990, the National Institute on Aging awarded approximately 19.4 percent of its approved applications; the award rate in FY 1989 was 25.6 percent.

EFFECT OF DOWNWARD NEGOTIATIONS

Mr. Early. What effect will these reductions, taken together, have on NIA's research program?

Dr. Williams. Downward negotiations have been utilized as a means for funding more competing research project grants. They do, however, slow the pace of research on aging. Many ongoing research initiatives are at junctures where delays or reductions in funding will result in further progress being delayed or halted.

RESEARCH OPPORTUNITIES

Mr. Early. What research opportunities could NIA support if additional funds were available?

Dr. Williams. If additional funds were available they would be used both to improve the level of funding for current programs and

to develop new programs and resources. These high priority opportunities include:

- o searching for the cause(s) of Alzheimer's disease, including studies of membrane structure, function, and transportation mechanisms in the aging central nervous system

- o developing better diagnostic techniques for Alzheimer's disease, including an easy and reliable biochemical diagnostic technique

- o development of new treatment and management methods for Alzheimer's disease, including the discovery of pharmacologic or biological agents that will safely, reliably, and effectively retard the progress or permanently interrupt the relentless course of the disease

- o enhanced funding for the Alzheimer's Disease Research Centers to expand the outreach efforts to rural, inner city and minority areas

- o training for careers in biomedical and biobehavioral research, basic research on the molecular, genetic and immunological basis of aging, geriatric medicine research and research on the neurosciences

- o additional Claude D. Pepper Geriatric Research and Training Centers to provide academic leaders to train sufficient numbers of qualified geriatric health care providers.

- o research on molecular mechanisms of cell death

- o identification, isolation, and characterization of longevity assurance genes

- o expansion of the colony of diet-restricted rodents

- o development of new animal models with specific advantages for studying aging, including a long-lived mouse model

- o studies of age-related changes in gene expression

- o additional clinical trials of promising new interventions to reduce frailty and injuries in older persons (the FICSIT trials)

- o studies on special problems associated with physical frailty in minority groups

- o developing and testing new approaches to treating and preventing osteoporosis and hip fractures--major contributors to physical frailty--in advanced age

- o research on other important strategies to reduce physical frailty, including rehabilitation of disabilities in older persons, and improved geriatric assessment techniques to identify persons who would benefit from rehabilitation

o responses to NIA's Request for Applications: "Pharmacology in Geriatric Medicine", which calls for research to improve medication prescribing options for older patients. Over 100 of these applications have been received, of which only approximately eight could be funded with resources currently designated for this initiative

o testing new approaches for treating and preventing urinary incontinence in older persons, as recommended by the recent NIH Consensus Development Conference on Urinary Incontinence

o studies on health special populations such as minority, rural, and mentally retarded or developmentally disabled older people as well as the oldest old

o research on related behaviors and life-styles, such as how older Americans and their families perceive and cope with life stressors, chronic conditions, and disabilities, strategies for promoting health-maintaining behaviors

o research on long-term care, including interventions to prevent and treat disabling conditions, in-home nd supportive services that foster independence, family care, forecasting the supply and demand for long-term care, and the economics of long-term care

o research to reduce the burdens of care for Alzheimer's disease, such as the nature and impact of caregiving burdens, the extent of informal and formal care, and interventions for reducing burdens of care

o studies of work, retirement, and health, including research on the availability of jobs for capable older people, optimizing the performance of older workers, facilitating adjustment to retirement, and providing productive roles outside of the labor force

o expansion of the Leadership and Excellence in Alzheimer's Disease award

o development of a stable source of carefully characterized normal aged and Alzheimer's disease post-mortem brain tissue

DOWNWARD NEGOTIATION OF CENTERS

Mr. Early. What has been the cumulative effect of the downward negotiations on the research programs of the Centers?

Dr. Williams. The Centers manage these reductions in a number of ways, including delay in recruitment of necessary technical and scientific staff, reduction of scope in research projects, and deletion or delay in the start of new projects. The downward negotiations reduce the momentum of the research effort, demoralize the senior scientific staff who spend more and more time searching for funds to maintain their laboratories rather than conducting research, and discourage junior investigators and post-doctoral fellow from entering research.

CLINICAL TRIALS

Mr. Early. Are there any high priority clinical trials which are ready but cannot be initiated because of a lack of funds in the budget request? If so, please provide a list of these, along with a brief description and the associated costs, including first year costs.

Dr. Williams. Yes, there are seven clinical trials that are ready to be initiated. The following is a list of these clinical trials, along with a description and cost.

Clinical Trial of Acetylcarnitine. This clinical trial will test the safety and efficacy of acetylcarnitine as a potential treatment for Alzheimer's disease. The first year cost of the trial would be $4.5 million, for a total of $20 million over the four year duration of the trial.

Clinical Trial of Nerve Growth Factor. Nerve growth factor is another potential treatment for Alzheimer's disease, and this trial would test its safety and efficacy as a treatment. The first year cost would be $5.5 million, for a total cost of $22 million over the four year duration of the trial.

Interventions to Decrease Aggressive or Agitated Behavior in AD Nursing Home Residents. Many Alzheimer's disease patients who are placed in institutionalized care express aggressive or agitated behavior, thereby increasing the difficulty of management. This trial would test various interventions to decrease this type of behavior. The planned duration of the trial would be five years at a total cost of $4.2 million; the first year cost would be $650,000.

Psychotrophic Management of Behavioral and Psychotic Symptoms in AD. Data based guidelines for the use of drugs to control secondary symptoms in dementing disorders--agitation, aggression, depression and sleeplessness--do not exist. Carefully designed and controlled clinical trials are needed to provide guidelines for use of many commonly prescribed medications to prevent the side effect of delirium in demented patients. Over a five year period, this trial would cost a total of $4.2 million, with first year costs of $650,000.

Reduction in the Burden of Care in Alzheimer's Disease. One of the major consequences of Alzheimer's disease is the tremendous burden their care places on both the primary caregiver as well as the professional caregiver. This trial would test innovative models of informal and formal health care and social supports, such as assessment of special AD units. The trial would cost a total of $15 million over a five year period; the first year cost would be $2.5 million.

Cognitive Interventions to Improve Intellectual Functioning. This trial will test the efficacy of short-term targeted training procedures in intellectual skills on long-term intellectual functioning. It would cost a total of $10 million over a ten year period. The first year costs would be $1.5 million.

Psychosocial Interventions for Improving Work Environments for Older Workers. This trial will test employee caregiving, fitness and retirement programs for older adults. The trial would last three years and cost a total of $5 million. The first year cost would be $1 million.

Mr. Early. Will you be funding any new clinical trials under your budget request?

Dr. Williams. We will not be initiating any new clinical trials under the FY 1991 budget request. We will provide funds only for those ongoing trials.

LEADERS IN GERIATRICS

Mr. Early. Dr. Williams, in the past we have discussed the need to develop a cadre of leaders in Geriatrics -- in basic and clinical research, in teaching and in primary care. Has this situation improved, deteriorated, or remained the same?

Dr. Williams. The number of well-qualified leaders in geriatrics is slowly increasing, but the gap between this number and that needed is widening. Numerous studies have found that the growing population of older persons will require many more geriatricians and other health care providers with geriatric training. The current shortage of well-qualified academic leaders in geriatrics severely limits the capacity to train these personnel. Because of this, the Institute of Medicine in 1987 recommended creating centers of excellence to train academic leaders in geriatrics. The recommendation for centers of excellence comes at a time of historic opportunity for geriatrics in the U.S.: three medical fields--internal medicine, family practice, and psychiatry--are establishing sub-specialties in geriatrics. Nearly every medical school in the U.S. is reexamining its curriculum in geriatrics. Thus the field is both ready for, and in need of, the expanded number of academic leaders who could be trained in these centers. If such leaders are not trained, the number and quality of trained geriatric personnel will suffer.

Accordingly, NIA has initiated support for the Claude D. Pepper Geriatric Research and Training Centers, and expanded career support opportunities for research fellows and junior faculty. NIA has funded two Claude D. Pepper Geriatric Research and Training Centers to date. While these will help relieve the shortage of geriatric academic leaders, alone they will not provide the numbers of skilled professionals which are desired.

PROJECTIONS OF ELDERLY POPULATION GROWTH

Mr. Early. What are the latest projections for growth of the elderly population?

Dr. Williams. A number of NIA supported researchers have developed projections of the elderly population in which the upper bound projections, especially for those aged 85 and over, far exceed

the official estimates developed by the Bureau of the Census. The Bureau of the Census develops the projections based upon their current estimates of the population below age 65 coupled with their estimates of the impact of net immigration and the projections of life expectancy provided by the Social Security Administration.

The most recent Census middle series projections estimate, for example, that the population aged 65 and over, currently estimated at about 32 million, will increase to 39 million in year 2010 and 68 million by year 2040. The same projection series estimates that the 85 and over population, the oldest old, currently about 3.2 million, will increase to 5.3 million in year 2010 and 12 million in year 2040. Under the Census estimates of higher life expectancy, the comparable figure for the 85 and over age group in year 2040 is 18 million, with the number aged 100 and over increasing from 58 thousand to 1.2 million.

Using different mortality assumptions, NIA supported researchers have plausible projections for the 85 and over age group that are far more extreme than even the Census highest estimates. One technique, assuming a continuing two percent per annum mortality decline, projects a total of 23.5 million persons in this age group by year 2040. Another approach that estimates the impact of risk factor control starting in year 2010 projects that there could be a total of 54 million people aged 85 and over by year 2040. A workshop that will discuss these striking differences is being organized for June 1990.

However, even in the Census's middle series the 85 and over age group is the fastest growing age group in the whole population, leading to the rapid aging of the older population itself. When the baby boom generation begins to turn age 85 after year 2030 this process will accelerate with the percent of the older population that is aged 85 and over climbing from 12.4 per cent in year 2030 to nearly 24 percent by year 2080.

INCIDENCE OF ALZHEIMER'S DISEASE

Mr. Early. How many people have Alzheimer's disease?

Dr. Williams. Current estimates indicate that nearly 4 million Americans suffer some form of AD. This number includes patients who have mild to severe forms of the disease. These numbers are somewhat larger than what previous studies indicated. There are several reasons for this upward trend in the numbers: previous studies were conducted 10 to 12 years ago when diagnostic criteria and instruments were not well developed; current studies include patients who not only are in care facilities but those at home; and it includes patients in all stages from the earliest to the most severe stages of the disease. Our feeling is that these numbers are under estimates and that the true numbers are much higher. The most important aspect of the current study is the future projections where the trend is upward. This trend is driven by the graying of America and is based on the demographic estimates derived from the National Center for Health Statistics and the U.S. Census Bureau estimates for older populations.

COST OF CARE FOR ALZHEIMER'S DISEASE

Mr. Early. Doctor, what is the current cost of care, etc. related to Alzheimer's disease?

Dr. Williams. A study conducted by NIA staff scientists indicates that the total annual cost of care is approximately $88 billion. Nearly half of this sum is direct out-of-the-pocket expenses. The rest are indirect cost such as loss of income and other less tangible factors. Often these economic cost estimates do not take into account two important factors associated with Alzheimer's disease: the clinical course of the disease or disability period ranges between 5 and 20 years and the financial cost of the disease is only a minor portion of the problem for the suffering family members, the true victims, who must endure distress for long periods.

Mr. Early. Can you give us some idea of what it will be 10 years from now?

Dr. Williams. The future projection of cost can only be pessimistic. Given the general trend in rising cost of health care, one can only estimate that the costs will double or triple depending on rates of inflation. The second major factor that will drive the national cost estimates up has to do with the increasing number of individuals who are expected to develop Alzheimer's disease. At present 4 million U.S. citizens are afflicted with AD. In 10 years, the number of individuals will approach 4.5 to 5.0 million.

FUNDING FOR ALZHEIMER'S DISEASE

Mr. Early. Doctor, how much will you spend on Alzheimer's research in FY 1991? How much will be spent NIH-wide?

Dr. Williams. The National Institute on Aging will spend approximately $94,878,000 in FY 1991 on Alzheimer's disease research. The National Institutes of Health will spend approximately $124,487,000.

POTENTIAL SAVINGS FOR ALZHEIMER'S DISEASE

Mr. Early. Doctor, how much could we save if Alzheimer's could be treated or prevented?

Dr. Williams. At present, it costs a minimum of $1,000 to $3,000 for a thorough diagnosis per Alzheimer's patient. Frequently this cost is repeated two or three times to verify the diagnosis. A simple improvement in our ability to positively diagnosis this disorder could reduce this process to a single visit to a doctor's office, thus cut the cost in half. As a very conservative estimate, this translates in cost savings of $1 billion a year.

If we find a treatment that could keep 10 percent of the patients out of nursing homes for one year, the cost savings will be approximately $8.8 billion a year.

BIOMARKERS

Mr. Early. Last year, we discussed NIA's initiative to develop a panel of biomarkers in aging. What progress has been made on this project and what are your plans for FY 91?

Dr. Williams. Fourteen investigators across the country are using the National Institute on Aging/National Center for Toxicological Research (NIA/NCTR) biomarkers of aging animal resource. These investigators are all working on parts of the effort to develop biomarkers ranging from DNA changes to behavioral changes in the whole organism. Although the research component of this effort is only in its second year, these investigators are already finding measures which are promising and relate cellular changes to whole organism changes. The NCTR has a comparable number of investigators using the colony to study biomarkers of toxicology. One unexpected consequence of the studies done so far, which have been reported in the literature and at national meetings, is the demand by other investigators for access to the colony of animals. To provide such access would require doubling the size of the colony. NIA and NCTR are prepared to take this step as soon as resources are available.

Mr. Early. How much has been allocated for this project in FY 1990 and FY 1991?

Dr. Williams. NIA allocated $1,021,101 in grant funds and $869,000 in contract funds for a total of $1,890,107 in FY 1990. For FY 1991, NIA has allocated $1,085,000 in grant funds and $958,500 in contract funds for a total of $2,043,500. These funds are needed for the maintenance of ongoing projects.

GERIATRICS AND PHARMACOLOGY

Mr. Early. Doctor, will you bring us up to date on NIA's activities in the area of drug prescribing practices and the elderly? If I remember correctly NIA had developed plans for clinical trials concerning state-of-the-art knowledge in geriatrics and pharmacology?

Dr. Williams. NIA has solicited proposals for clinical trials and other research in geriatric pharmacology in its Request for Applications: "Pharmacology in Geriatric Medicine," published in the NIH Guide for Grants and Contracts in August 1989. This calls for research projects on detection of previously unrecognized adverse drug effects and ways to prevent them, development of new medications for age-associated diseases, techniques to improve physicians' prescribing practices and use of drugs by patients, and development of research-based guidelines for the withdrawal of medications from older persons so that only those medications required are continued.

These research projects will be funded in FY 1991. More than 100 applications have been submitted, illustrating the importance of this area and the interest from the research community. We expect that resources will permit funding only approximately eight of these projects.

Current NIA research findings reinforce our belief in the value of this type of research. For example, an NIA-supported study conducted in Nashville, which recently appeared in the Journal of the American Medical Association, showed that use of some tranquilizers, but not others, was associated with higher rates of falling leading to hip fractures in older persons. This information could be translated directly into better drug prescribing. Since the annual cost of hip fractures exceeds $7 billion, a decrease of only 15 percent resulting from better prescribing would save over $1 billion in health costs, not to mention reductions in disability. Another NIA-supported study by San Francisco researchers showed that one anti-ulcer medication commonly used by older persons increases the risk of fainting and falls in those also taking certain blood pressure medications, whereas another anti-ulcer drug did not have this effect. These are only two examples of numerous previously unrecognized drug effects which could be revealed by this type of research, which could lead to significantly improved geriatric care and lower unnecessary health costs.

DRUGS FOR TREATING ALZHEIMER'S DISEASE

Mr. Early. What progress can you report since last year in identifying drugs that may be effective against Alzheimer's disease?

Dr. Williams. Currently, there are 16 drugs in various stages of pilot or preliminary study for the treatment of AD. One of these, acetyl-l-carnitine, has proved effective in improving memory in animal studies. The precise mode of action is not known. It has been shown to have some cholinomimetic action, but more importantly it seems to improve mitochondrial metabolic activity. There is an accumulation of evidence that AD may be a reflection of a systemic metabolic effect due to specific defects in mitochondrial enzyme systems. Acetyl-l-carnitine has been shown to stabilize the cognitive functions of AD patients over a 12-month study period.

Another drug under preliminary study is nimodipine. Nimodipine is a calcium antagonist, approved for the treatment of strokes, which may prevent membrane changes that interfere with learning. Preliminary evidence from aging rabbits and from people suffering from strokes, indicates that nimodipine may improve memory and possibly restore cognitive function.

Studies in animals indicate that nerve growth factor (NGF) can prevent injury-induced degeneration of cholinergic neurons and improve cognitive functions. NGF may prove to be a valuable treatment alternative for AD. The NIA held a workshop in 1988 on the possible use of NGF in the treatment of AD. Among the conclusions of that workshop were that before human trials are initiated, further preclinical studies in non-human primates are needed to determine toxicity and drug delivery systems, as well as that a reliable source of well-characterized NGF be made available. In light of the progress towards achieving these ends, the NIA is planning to hold another workshop this year to reconsider the status of NGF as a potential treatment for AD.

Huperzine-A is a novel alkaloid compound isolated from the plant Huperzia serrata, the leaves of which have long been used in China as a "memory tea" prescribed by herbalists for failing memory. This compound has now been synthesized. It appears to function as a highly efficacious cholinesterase inhibitor; it increases the action of acetylcholine by retarding its enzymatic degradation as does THA. Since huperzine-A has been investigated in double-blind trials in China for the treatment of AD and reported to be efficacious, serious consideration should be given to the biological, safety and, behavioral assessment of this agent in this country.

NEW INITIATIVES

Mr. Early. Will any significant new initiatives or opportunities be lost or delayed by lack of funds in the FY 91 budget request? Please provide, for the record, a list of these along with a brief description and the funding requirements associated with each.

Dr. Williams. If additional funds were available, the NIA would be able to implement several new research initiatives. Among these are:

Additional Frailty Clinical Trials. Trials of promising new interventions to reduce frailty and injuries in older persons (the FICSIT trials) are needed. $2,600,000 per year.

Treating Urinary Incontinence. A recent NIH Consensus Development Conference on Urinary Incontinence recommended testing new approaches for treating and preventing urinary incontinence in older persons. $5,000,000 per year.

Age-related changes in gene expression. The goals are to identify differentially expressed genes in mature versus senescent cells which could explain age-dependent changes in cell/tissue/organ structure and function. Once these genes are identified they will be cloned to determine whether they contain regulatory regions which are responsible for the differential expression. Finally, regulatory factors would be identified. $1,000,000 per year.

Molecular mechanisms of cell death. Cell death can occur due to environmental stress or as a result of programmed cell death especially during organ development. What is not known is whether these two processes share a common pathway, and if so what the common steps are. At what point is this pathway irreversible, and what can be done to protect cells from reaching this irreversible state. Knowledge about this should provide insight into the age-related loss of cells which may impair the normal functioning of organs and tissues. $600,000 per year.

Biology of aging skin. Skin not only provides an attractive model system for studying aging changes, but also is an area where intervention should be possible. For example, longitudinal, relatively non-invasive studies are practical, and the potential for developing reliable biomarkers of aging is high. Another benefit of this research is the expected identification of fundamental and cell-specific regulatory mechanisms of aging. $1,250,000 per year.

Development of a long-lived mouse model. The purpose of this is to facilitate the identification, isolation, and characterization of longevity assurance genes in a mammal. The project involves using natural selection to develop a long-lived mouse strain which will then be characterized to determine what other physiological changes co-vary with extended life span. These changes will then be correlated with genetic changes that occurred during the selection. Development of such a model would require about $1,000,000 per year for about 10 years.

Colony of calorically-restricted rodents. Reduction of the caloric intake of an animal, while maintaining all essential dietary nutrients, increases the life span of the animal while also delaying the onset of cancer and other age-related diseases such as kidney disease. A source of these animals is in high demand by the research community, but is not currently available. It is not cost-efficient for most investigators to maintain their own colony of these animals, so it is important that the NIA support such a facility for use by investigators doing research on aging. $1,000,000 per year.

Alternative animal research. Most research on aging in animals is currently done using rats, mice, and fruit flies. However, other animals provide certain advantages, but for a variety of reasons have not been developed for widespread use. For example, hamsters are much less likely to develop the tumors and kidney disease that plague research with mice and rats, and birds might provide a good model for the study of osteoporosis because of the high demand for calcium during egg laying. The NIA believes that the establishment of a limited number of alternative animal colonies would enhance progress in a variety of research ares. $750,000 per year.

Aging rural populations. Research is needed for examining the life-long experience, the current circumstances, and the special physical and social nature of rural life as they affect the health, well-being, and functioning of rural older people. This includes such topics as the changing sociodemographic and epidemiologic characteristics of older rural populations, the occupational and physiochemical environment, the population aging of rural communities, the availability, utilization, and quality of health-care and other social services, and aging rural people as resources. $1,750,000 per year.

Work, retirement, and health. Research is needed on the many millions of older Americans who now spend 2 to 3 decades of their lives in retirement. The majority of retirees are vigorous and constitute an untapped national resource: some 2 million retirees, aged 50-64, have been identified as capable and interested in getting jobs. Moreover, NIA-supported research demonstrates that active participation not only increases older people's productivity and independence, but also improves their health and intellectual functioning. A deeper understanding of work and retirement is required in such areas as job availability for older workers; optimizing the performance of older workers; facilitating adjustment to retirement and productive roles outside the labor force; and

sustaining productivity and functioning among frail retirees. $3,500,000 per year.

"Elder-friendly" environments. Countless everyday activities present serious threats to frail older people--preparing meals, shopping, taking a bath, driving a car, using an automatic bank teller. Human factors research, adapted from space technology, is needed as a knowledge-base that can help prevent injuries, extend working life, enhance independence, and reduce demand for long-term care. Research is needed on improvements in transportation, communication, housekeeping and work environments, and health-care environments and equipment. $2,000,000 per year.

RESEARCH PRIORITIES

Mr. Early. If an increase over the FY 91 budget request is provided, how would you use these additional funds? What would your priorities be?

Dr. Williams. If additional funds were available, they would be used both to improve the level of funding for current programs and to develop new programs and resources. These high priority opportunities include:

o searching for the cause(s) of Alzheimer's disease, including studies of membrane structure, function, and transportation mechanisms in the aging central nervous system

o developing better diagnostic techniques for Alzheimer's disease, including an easy and reliable biochemical diagnostic technique

o development of new treatment and management methods for Alzheimer's disease, including the discovery of pharmacologic or biological agents that will safely, reliably, and effectively retard the progress or permanently interrupt the relentless course of the disease

o enhanced funding for the Alzheimer's Disease Research Centers to expand the outreach efforts to rural, inner city and minority areas

o additional Claude D. Pepper Geriatric Research and Training Centers are needed to provide the geriatric academic leaders to train sufficient numbers of qualified geriatric health care providers.

o additional frailty clinical trials of promising new interventions to reduce frailty and injuries in older persons are needed.

o develop geriatric assessment techniques to identify treatable and preventable disability

o improved medication prescribing

- o testing new approaches for treating and preventing urinary incontinence in older persons

- o developing and testing new approaches for treating and preventing osteoporosis and hip fractures in advanced age

- o studies of special problems associated with physical frailty in minority groups

- o development of new techniques for geriatric rehabilitation

- o training for careers in biomedical and biobehavioral research, basic research on the molecular, genetic and immunological basis of aging, geriatric medicine research and research on the neurosciences

- o research on molecular mechanisms of cell death

- o identification, isolation, and characterization of longevity assurance genes

- o expansion of the colony of diet-restricted rodents

- o development of new animal models with specific advantages for studying aging, including a long-lived mouse model

- o studies of age-related changes in gene expression

- o additional clinical trials of promising new interventions to reduce frailty and injuries in older persons (the FICSIT trials)

- o studies on special problems associated with physical frailty in minority groups

- o developing and testing new approaches to treating and preventing osteoporosis and hip fractures (major contributors to physical frailty) in advanced age

- o research on other important strategies to reduce physical frailty, including rehabilitation of disabilities in older persons, and improved geriatric assessment techniques to identify persons who would benefit from rehabilitation

- o responses to NIA's Request for Applications: "Pharmacology in Geriatric Medicine", which calls for research to improve medication prescribing options for older patients. Over 100 of these applications have been received, of which only approximately eight could be funded with resources currently designated for this initiative

- o testing new approaches for treating and preventing urinary incontinence in older persons, as recommended by the recent NIH Consensus Development Conference on Urinary Incontinence

o studies on health special populations such as minority, rural, and mentally retarded or developmentally disabled older people as well as the oldest old

o research on related behaviors and life-styles, such as how older Americans and their families perceive and cope with life stressors, chronic conditions, and disabilities, strategies for promoting health-maintaining behaviors

o research on long-term care, including interventions to prevent and treat disabling conditions, in-home and supportive services that foster independence, family care, forecasting the supply and demand for long-term care, and the economics of long-term care

o research to reduce the burdens of care for Alzheimer's disease, such as the nature and impact of caregiving burdens, the extent of informal and formal care, and interventions for reducing burdens of care

o studies of work, retirement, and health, including research on the availability of jobs for capable older people, optimizing the performance of older workers, facilitating adjustment to retirement, and providing productive roles outside of the labor force

o expansion of the Leadership and Excellence in Alzheimer's Disease award

o development of a stable source of carefully characterized normal aged and Alzheimer's disease post-mortem brain tissue

ADVANCE IN SCIENTIFIC TECHNOLOGY

Mr. Early. I understand that a device aimed at analyzing brain chemistry has been developed, which has significant implications for studies on Alzheimer's disease, Huntington's, and other brain disorders. Doctor, what can you tell us about this advance in scientific technology? Didn't NIA support work on this device with a Small Business Innovation Research award?

Dr. Williams. This device is a sophisticated high performance liquid chromatography system that allows simultaneous analysis of a large number of compounds in blood, cerebrospinal fluid, or other properly prepared tissue extracts. It was developed with the assistance of a Small Business Innovation Research grant though the Division of Research Resources, and has received initial evaluation at Harvard University Medical Institutions. It can be counted as one of the successes of this program, having gone through research and development to commercial availability. One of the investigators funded by NIA has been using it in his research. This instrument offers the promise of research as well as diagnostic potential and is one of the growing armamentarium of research instruments to analyze the aging nervous system and neurodegenerative diseases.

ADVISORY PANEL ON ALZHEIMER'S DISEASE

Mr. Early. The Advisory Panel on Alzheimer's disease has issued its first report. Briefly review for us its recommendations with respect to biomedical research. To what extent does your budget request include funds to carry out these recommendations?

Dr. Williams. The Advisory Panel on AD recommended several areas of biomedical research, including areas such as: identifying the causes of AD; elucidating the sequence of pathological changes in the brain; developing better diagnostic screening tests; trying to determine the role of genetic factors on the disease; population studies designed to determine selection risk factors; work on the neurochemistry of the disease; attempts to determine the structure and function of abnormal proteins; the role of excitotoxins; nerve growth factors and infective agents in causing the disease; and more work in developing better non-invasive diagnostic methods such as PET, MRI and SPECT. The panel also urged more research on clinical studies, including work on improving neuropathological indices of the disease. Clinical trials to test the efficacy of new drugs and more cross-national epidemiological studies were also recommended by the Panel.

The NIA program on Alzheimer's disease is the most comprehensive within the public health service. It includes work on fundamental biological basis of the disease, diagnosis, treatment, patient care and management, clinical trials, epidemiology, psychosocial factors, and international or cross-cultural issues. The NIA budget request for Alzheimer's disease in FY 1991 is $94,878,000 compared to the $300 million recommended by the Panel.

TEACHING NURSING HOME PROGRAM

Mr. Early. Doctor, bring us up to date on the activities of the Teaching Nursing Home Program. What has NIA learned from these projects?

Doctor Williams. The number of NIA's Teaching Nursing Home (TNH) Awards has increased from two in 1982 to seven at present. Research productivity of the TNHs has been strong, with over 50 original-data papers in peer-reviewed journals to date. As the program has evolved, TNH research emphases have expanded from clinical epidemiology to include pathophysiologic studies and most recently, intervention studies. Thus the program has provided a sound base for developing better long term care. A second benefit has been increased sophistication in methods of conducting research in nursing homes. TNHs have also been disseminated this knowledge through several publications.

Some example of clinical advances from NIA's TNH research program include:

Discovery of New Cause of Urinary Incontinence. A study at the Harvard/Hebrew Rehabilitation Center TNH suggests that a previously unrecognized abnormality in function of the detrusor (bladder muscle) may cause incontinence in many nursing home residents and possibly many older persons in the community. The abnormality has

been termed "detrusor hyperactivity with impaired contractile function" (DHIC), and was found in one-third of incontinent patients in a nursing home study. In DHIC, uncontrolled bladder contractions occur, but the bladder is too weak to empty completely. This poses particular problems for treatment, since patients with DHIC may be particularly prone to urinary retention and its elevated risk of urinary tract infections if their incontinence is treated with drugs to suppress the uncontrolled bladder contractions. This discovery may lead to more effective treatment for older persons with this condition.

Increasing Independence through Strength-Building Exercises. Studies at the Harvard/Hebrew Rehabilitation Center TNH in very old frail nursing home residents--average age 90 years--show that eight weeks of leg strength training markedly improved their limited walking ability, both in speed and distance. The improvement was associated with doubled leg muscle strength and significantly improved muscle size. This is one of the key findings providing the basis for NIA's new Frailty Clinical Trials which will test techniques to reduce dependency and injuries in frail older persons.

Therapy for Asymptomatic Bacteriuria in Older Women. Asymptomatic urinary tract infections are extremely common among older women. This asymptomatic bacteriuria may be associated with increased mortality risk. The efficacy of conventional antimicrobial therapy in treating these infections has been controversial. A controlled study conducted by an NIA Teaching Nursing Home in Philadelphia determined that a short course of the antibiotic trimethoprim, with cefaclor as a "step 2" drug, was an effective treatment for asymptomatic bacteriuria in a group of older women, mean age 86 years. After six months of follow-up, the treated group had significantly less asymptomatic bacteriuria and fewer symptomatic infections, suggesting that this approach may prevent symptomatic infections in this population.

Exercise Protects Against Cardiovascular Disease in Advanced Age. Another study by the Philadelphia NIA Teaching Nursing Home demonstrated that exercise can prevent significant cardiovascular disease even in advanced age. A group of older men and women without previous symptomatic cardiovascular disease were divided into two groups. One participated in a bicycle exercise program; the other did not exercise regularly. After two years, only 4 percent of the exercise group suffered significant cardiovascular events such as angina, heart attacks, heart failure, and abnormal heart rhythms, compared to 19 percent of the group which did not exercise. This study indicates that appropriate exercise could markedly reduce the significant mortality, hospitalizations, and disability from cardiovascular disease among older persons.

Leg Weakness as a Cause of Falling: Pathologic Basis. A study at the Albert Einstein College of Medicine TNH in New York demonstrated that severe ankle weakness is an important cause of falls, suggesting that muscle strengthening programs may be effective in reducing falls as well as improving functional status. The research team also found that those with severe ankle weakness has unusual neurologic changes, shown in brain CAT scans, suggesting that some types of muscle weakness in old age may be caused by a

previously unrecognized, and potentially treatable, neurologic disorder.

Mr. Early. How many Teaching Nursing Home projects are now being funded and how many do you plan to fund?

Doctor Williams. The NIA currently funds seven Teaching Nursing Home projects. There is no set number which is proposed for funding. The TNH program remains an NIA priority, and we encourage additional TNH applications.

AIDS IN THE OLDER POPULATION

Mr. Dwyer. Various agencies within the Public Health Service have begun to focus their attention on the particular problems of pediatric AIDS, and the impact this terrible disease has on developing body systems. AIDS, however, has also tragically impacted individuals on the other end of the age spectrum. It is my understanding that over 10% of all AIDS patients are over the age of 50. How many individuals over the age of 50 are sero-positive for HIV?

Dr. Williams. The numbers of sero-positive cases are unknown. However, the diagnosed AIDS cases are believed to be only the tip of the iceberg of infected cases. The Centers for Disease Control reported 7,527 cases of people aged 50 and over actually diagnosed with AIDS, as of September, 1988. Of these diagnosed cases, 1,008 were aged 65 and over.

Mr. Dwyer. What is the most prevalent form of transmission for AIDS patients over 50? Does it mirror those for younger adults?

Dr. Williams. In 64 percent of the cases, homosexual and bisexual males constitute the primary source of transmission for those 50 and older, very similar to the total for all ages, which is 70 percent. For the 50 plus age group, blood transfusion is second largest cause, representing 16 percent as contrasted with only 3 percent for all ages, and drug abusers are third where 10 percent are 50 years of age or older compared to 26 percent for all ages.

Very different is the special category of cases aged 65 and over, for which blood transfusion is the major source, 55 percent, and homosexual/bisexual males is second, 27 percent.

Mr. Dwyer. Pediatric AIDS is different from adult AIDS, because of the immaturity of body systems. Does the elderly AIDS patient suffer unique problems because their other body systems are beginning to decline?

Dr. Williams. While there are similar problems of lack of immunologic competence in newborn infants and elderly individuals, these stem from different causes. In infants the cellular immune system is still immature, and its development is very much dependent upon the correct functioning of the thymus. This tissue is large and soon after birth becomes very active, producing thymus-derived T lymphocytes, which are distributed to the whole immune system, and are involved in both cellular and antibody reactions. When T helper cells, still not produced at optimal levels, become infected with HIV prior to or at birth, the whole immune system is compromised. AIDS is able to develop faster, and opportunistic infections are worse, due to lack of defenses. Much information is available about thymic function in the newborn, both in humans and in animal model systems, and much research is being done on this stage of immune function.

In contrast, in elderly individuals the thymus is almost completely absent, although the remnants still have considerable importance in seeding T cells to the peripheral lymphoid system.

The types of T cells present are different than those found in younger individuals, with fewer helper, cytotoxic and suppressor T cells, and more of undetermined, or no, clear function. General immune function is decreased, as is shown by increased susceptibility to infectious diseases, including pneumonia, zoster, cytomegalovirus and fungal infections, and the development of cancer, including Kaposi's sarcoma. Until AIDS arrived, many of these were diseases which were found only in severely immuno-compromised, mainly elderly individuals. In elderly individuals the normal regulatory collaboration of T cells with antibody producing B cells is frequently impaired. Infection by HIV of T helper cells, already present in reduced numbers, only reduces immune resistance further, speeding up the development of AIDS-related Complex (ARC) and full-blown AIDS. The consequent diseases appear more easily and are more difficult to control, due to the decline in general competence of bodily functions, including immunological, kidney and liver functions. It has been found in HIV-infected persons older than 55-60 years of age that once they seroconvert, producing anti-HIV antibody, any infection that they suffer is likely to be fatal. In addition, in the elderly, the frequently observed reduced tolerance to drugs and a decline in the ability to detoxify chemotherapeutic agents used to treat AIDS and other diseases makes treatment even more difficult.

As yet only a few researchers are specifically examining immune and other physiological functions in geriatric populations, and even fewer in HIV-infected elderly. Much remains to be done in these areas, both in "normal" as well as old people with chronic diseases, those infected with HIV, and those with AIDS itself.

Mr. Dwyer. As you know, elderly persons are more likely to be on prescription medications than younger people. Has there been any study of the interaction of AIDS drugs like AZT and DDI and drugs used to treat hypertension, arthritis, and other diseases which affect older Americans?

Dr. Williams. NIA has not supported any studies specifically on the problems of anti-HIV drug therapy in the elderly either in terms of drug interactions or the effects of age related hepatic and renal dysfunction on the metabolism of anti-HIV medication. Since both AZT and DDI, as well as the new drugs, have very serious side effects, it is important that this information be available. As part of the ongoing study of AIDS in the elderly patient, NIA intramural research has identified and followed patients in the AIDS clinic at Johns Hopkins who are over the age of 60. The effects of AZT on this group are being monitored but a more extensive study of this problem is planned for the future.

AIDS CLINICAL TRIALS

Mr. Dwyer. AIDS Clinical Trials now include a greater number of women and children. Have efforts been made to include older HIV-infected Americans in clinical trials?

Dr. Williams. To our knowledge, the elderly have never been excluded from any of the clinical trials of AZT or DDI, but there has not been a trial designed to address the specific problems of

HIV drug therapy in the elderly. Since HIV-caused illness is so serious and influences the function of many organ systems, therapy is usually directed to conditions that are causing the most problems. Overall evaluation of the patient with the purpose of providing care for both HIV-induced illness and age related problems has not been undertaken.

COLLABORATION WITH NIAID ON AIDS

Mr. Dwyer. Has NIA been working closely with NIAID on the special needs of older AIDS patients?

Dr. Williams. In conjunction with an NIAID-funded AIDS treatment and research facility at Johns Hopkins, NIA scientists have formed a combined AIDS-Geriatric Medicine clinic and provided research proposals for the study of the special problems of the older HIV-infected individual. NIA also has close working contacts in AIDS research with the Centers for Disease Control, the National Institute of Mental Health, the National Academy of Science's AIDS Committees, the National Institute of Child Health and Development, and indirectly with other Institutes through the NIH Office of AIDS Research, the NIH AIDS Executive Committee, the NIH Prevention Committee, and the NIH Working Group on Health and Behavior.

REDUCING FRAILTY AND INJURIES IN OLDER PEOPLE

Mr. Dwyer. It is my understanding that NIA and NCNR are collaborating on a research initiative to reduce frailty and injuries in older people. Our country is aging at a rapid rate, and the frail elderly over age 85 is one of our fastest growing groups. What areas of research are currently being funded by the NIA/NCNR joint venture?

Dr. Williams. These Frailty Clinical Trials, collectively known as FICSIT ("Frailty and Injuries: Cooperative Studies of Intervention Techniques") have the goals of reducing dependence, injuries and long term care needs by reducing physical frailty, that is, severely impaired strength, mobility, balance, and endurance, and falls. Interventions to be tested include leg strengthening, balance and flexibility training, other rehabilitation strategies, nutritional interventions, fall and hip fracture prevention programs, and environmental/ behavioral strategies.

As I noted at an October 1989 briefing requested by the U.S. Senate and House Committees on Aging, the Frailty Clinical Trials (FICSIT) can have a major impact on dependence and long term care needs. These interventions could significantly increase older persons' abilities to live independently, and prevent falls and disabling injuries such as hip fractures. Since physical frailty afflicts literally millions of older Americans, the potential public health benefits and reductions in long term care burdens are enormous. The studies will provide information for both community-dwelling and institutionalized older persons. Because the FICSIT trials will look at several critical outcomes such as functional status, mobility, general health, falls, and many others in a coordinated way, the findings can be expected to offer critically

needed knowledge on ways to reduce dependency and improve the quality of life of older persons.

However, the Frailty Clinical Trials (FICSIT) will test only a segment, albeit a very important one, of potential interventions against frailty. Because of the huge scope of this problem, NIA has organized a comprehensive long range research program aimed at continuing reductions in frailty and the care burdens it imposes. Other components of NIA's frailty research program include:

o Geriatric Rehabilitation. Millions of frail older persons could be restored to greater independence by rehabilitation, but better techniques are needed, especially for the 200,000 hip fractures occurring each year in older persons. Besides its Frailty Clinical Trials initiative, NIA has solicited proposals for biomedical and psychosocial research needed to achieve the enormous potential of geriatric rehabilitation. In 1990, NIA will also address a serious need for researchers with combined expertise in rehabilitation and aging by introducing special research career awards in this area.

o Geriatric Assessment. A recent NIH Consensus Conference panel noted the value of geriatric assessment in improving health outcomes and reducing health costs, and recommended research to improve assessment strategies further. Such strategies are crucial for improved long term care eligibility and reimbursement policies, since they could identify persons with treatable or preventable disabilities, for whom proper treatment and services could reduce long term care needs. Several approaches are ready for testing.

o Frailty in Minorities. Genetic and environmental factors affect risks for disabling diseases and abilities to cope with frailty and its consequences. To develop effective strategies to reduce frailty and disability among minorities, we need to learn more about the effects of these factors in different groups.

o Improving Medication Use Among Frail Older Persons. Geriatric patients often take several drugs whose side effects worsen frailty by impairing balance, orientation, and daily activities. Congressional hearings have highlighted severe health problems and costs due to poor drug prescribing for older persons. NIA has solicited proposals for research to provide solutions to this problem. About 100 applications were received, at least 25 of very high quality.

o Urinary Incontinence (UI). UI afflicts five million older Americans, and causes over $10.3 billion per year in health care and related costs. UI is a serious cause of disability and long term care needs among frail older persons. It afflicts half of nursing home residents. NIA's UI research program involves urologists, gynecologists, geriatricians, behavioral scientists, and nurses at numerous sites. This research has produced significant advances in treatment, but only a fraction of the potential for improvement. A 1988 NIH Consensus Conference on Urinary Incontinence recommended a major research initiative on UI. NIA's 1989 solicitation for research proposals in response to these recommendations has engendered considerable interest from the research community.

o Fundamental Progress on Chronic Musculoskeletal Diseases and Disorders of Gait and Balance. Physical frailty would be dramatically reduced by better treatments for degenerative diseases which impair physical functioning among older persons. NIA has established a major osteoporosis program, focused particularly on preventing hip fractures. Clinical trials are now feasible in this area, requiring approximately $6 million per year above current osteoporosis research support levels. Promising opportunities for progress against osteoarthritis, degenerative muscle conditions, and age-related disorders of gait and balance also merit increased research.

In summary, NIA has established a very active program on geriatric physical frailty which reflects a serious, long-term commitment to this critical area of inquiry. Progress in the above areas should lead to major reductions in dependence and long term care needs of older persons.

OSTEOPOROSIS

Mr. Dwyer. Will any of these studies be concentrating on osteoporosis, a disease responsible for approximately 1.3 million fractures annually?

Dr. Williams. Of the 42 applications evaluated for possible funding as FICSIT sites, none of the eight most highly rated proposals concentrated on osteoporosis and bone parameters as a primary outcome measures. There were three other proposals judged to be very good which sought to increase bone strength via exercise, hormonal and/or nutritional intervention; however, available funds did not allow us to fund these very important and timely proposals.

An ongoing project in NIA's osteoporosis program is testing calcium supplementation to prevent bone loss in older women, following up on preliminary findings suggesting surprisingly high effectiveness of this approach. However, this is only one of several promising approaches which are ready for testing, and need testing in older persons, who are most adversely affected by osteoporosis.

Mr. Dwyer. Will you additionally be coordinating your efforts with NIAMS research into rheumatoid and osteoarthritis?

Dr. Williams. Although NIAMS is not formally involved in the FICSIT trials, we have collaborated with NIAMS in the past in promoting research on osteoarthritis. A joint program announcement on this topic has been issued has been issued.

COORDINATION WITH NINDS

Mr. Dwyer. Will you be coordinating your efforts with NINDS research into efforts to improve the functional capacities of those elderly who have suffered stroke?

Dr. Williams. The NIA program staff have the responsibility to convene the NIH Coordinating Committee on Alzheimer's disease. The Committee meets on a regular basis at least once a month. Members

of the committee include the staff of the National Institute of Neurological Diseases and Stroke and the National Institute of Mental Health as well as the Food and Drug Administration. Some of the scientific effort directed at the NIA on AD has a direct bearing on the condition of stroke victims. The staff from both Institutes work closely in coordinating their efforts in those areas where there is mutual interest.

COST OF ALZHEIMER'S DISEASE

Mr. Dwyer. The tragedy of Alzheimer's disease and related dementias is a growing one. It is the fourth leading cause of death for adults, and it is estimated that it may afflict 14 million Americans by the year 2050. What is the annual cost of Alzheimer's disease in the U.S.?

Dr. Williams. According to a study conducted by NIA staff scientists, the total annual cost of care is approximately $88 billion. However, this figure may double or triple, depending on the rates of future inflation and increased health care costs.

BUDGET FOR ALZHEIMER'S DISEASE

Mr. Dwyer. How much will NIA spend this year to combat Alzheimer's and related dementias?

Dr. Williams. The total NIA budget to combat AD in FY 1990 is estimated to be approximately $91,264,000. In FY 1991, it is projected to be $94,878,000.

RESEARCH ON ALZHEIMER'S DISEASE

Mr. Dwyer. In light of the growing problem of Alzheimer's, and its potential impact on so many individuals, has NIA accelerated its research on this terrible disorder?

Dr. Williams. The battle to combat Alzheimer's disease is the number one priority of the NIA. The problem of AD is approached in a very comprehensive manner at NIA. The assault includes several fronts covering basic biomedical studies and clinical studies, as well as psycho-social factors.

AIDS-RELATED DEMENTIA

Mr. Dwyer. As you know, there is also a terrible dementia which afflicts individuals with AIDS. Will NIA and NIAID collaborate on research efforts to determine if there is any relation between AIDS-related dementia and Alzheimer's?

Dr. Williams. The NIA is interested in understanding the causes of neurodegenerative diseases associated with aging, most clearly typified by Alzheimer's disease. The study of AIDS dementia may provide some research clues and opportunities for a more general understanding of the processes associated with dementia. There are formal and informal channels of communication between NIA and NIAID. The NIAID is one of the supporting Institutes for the NIH Alzheimer's Disease Coordinating Committee. As opportunities arise,

it has been the history of the NIH for the Institutes to cooperate and collaborate to solve common problems.

BONE AND MINERAL DISEASE

Mr. Porter. I am interested in the level of NIA research related to bone and mineral disease. Please provide for the record a listing of NIA supported intramural and extramural research, and the level of funding, in each of the following areas -- Osteoporosis, Primary Hyperparathyroidism, steroid induced bone disease?

Dr. Williams. In FY 1989, NIA supported 36 osteoporosis research projects totalling over $7.6 million per year. NIA also supported an additional 19 research projects on osteoporotic fractures and risk factors for such fractures, totalling over $3.4 million per year. Thus, in FY 1989, NIA expended $11.1 million in support of osteoporosis and related research. In FY 1990, we will support $11.5 million in osteoporosis and related research; the amount in FY 1991 will be $12 million. The NIA does not currently support research on primary hyperparathyroidism or steroid-induced bone disease.

Mr. Porter. Do you have any data on the frequency of these diseases? If so, would you provide it for the record?

Dr. Williams. Osteoporosis affects over twenty million people in the U.S. including one-half of women over 45 and 90 percent of those over age 75, as well as large numbers of older men. One-third of women over age 65 suffer osteoporotic spinal fractures; one-third of women and one-sixth of men will suffer osteoporotic hip fractures by the time they are 90. Of the more than 227,000 hip fractures that occur in the U.S. every year, almost 50 percent occur in persons 80 years of age or older. There is an alarming 12 to 20 percent mortality rate from hip fracture and 20 percent of the survivors will be admitted to nursing homes, often for the rest of their lives.

DISSEMINATION OF INFORMATION THROUGH AOA

Mr. Porter. The Administration on Aging (AoA) provides an effective conduit for disseminating research findings developed at NIA. Please describe your efforts to disseminate information through AoA.

Dr. Williams. The NIA's effective information dissemination program has long used the Administration on Aging's network of state and area agencies on aging. These agencies routinely receive NIA materials in bulk quantities. In turn, they distribute NIA publications to local organizations and individuals. Publications such as the Age Page are effectively disseminated through this conduit--a process that is cost-effective and avoids unnecessary duplication of effort. The AoA also actively supports NIA's information efforts in Alzheimer's disease and will be working with the newly formed Alzheimer's Disease Education and Referral Center.

The NIA-AoA collaboration offers the public the opportunity of benefitting from the expertise and resources of two key federal agencies. Should NIA be given resources to develop a clearinghouse that would disseminate information on healthy aging, this existing

collaboration would form a solid basis for creating effective linkages on the local level.

NATIONAL CONFERENCE ON ALZHEIMER'S DISEASE

Mr. Porter. In FY 1988, AoA and NIA co-sponsored a national conference program on Alzheimer's disease. Would you please describe the conference? How have you followed up on that conference?

Dr. Williams. During the period of 1988 to 1989, approximately 20 conferences were organized and sponsored by NIA and the Administration on Aging. These conferences were all planned and conducted by the 15 Alzheimer's Disease Research Centers. They were designed to provide the latest information on health care delivery and to address research issues concerning this subject. Some of these conferences are in the process of being published as journal articles and books. From all accounts, the conferences were extremely successful in transferring the latest knowledge on delivery of care issues to primary care providers, as well as family members. We at NIA have been encouraged by the success of these conferences and hope to continue this effort.

HEALTH AND RETIREMENT SURVEY

Mr. Young. Dr. Williams, as the representative of more older Americans than any other member of the House, I am concerned about the lack of a good, sound statistical base on which we need to make many of the decisions about funding for programs such as the Older Americans Act, aging research, and health care. Researchers in the field tell me our best data base for information about older Americans is more than 20 years old. Recognizing the need for better, more reliable information in this area, our Committee last year directed the National Institute on Aging to begin planning for a major, new longitudinal Retirement and Health Survey. What funding have you committed to this project in the current fiscal year and what are your goals for this initial stage of the study?

Dr. Williams. The Institute recently issued an Request for Applications calling for a Cooperative Agreement for the new Health and Retirement Survey, with a start date of September 1990. The Institute has committed $500,000 for the first year of the study which will constitute the design and planning phase. The study, as designed, should be able to provide data needed at the federal and regional level for planning retirement policies.

Mr. Young. Dr. Williams, what funds are included in your 1991 budget request for this project and what are your goals for this phase of the study? Is this amount of funding sufficient to meet your goals?

Dr. Williams. The second phase will begin in FY 1991 at a cost of $2,000,000. However, the FY 1991 budget request contains $550,000 for this survey. The next phase, which is expected to last at least another four years, will include drawing the actual study respondents from a national sampling frame and completing the interviewing for the baseline and one follow-up interview. The funds requested are estimated to be adequate for the basic study. These funds would not provide for any over sampling of minorities or of special regions such as the sunbelt.

Mr. Young. Dr. Williams, in discussing this study with professionals in the field, concern has been expressed to me that while a national survey of older Americans is important, it will not provide a large enough statistical base for any one geographical area to best gauge questions about migration patterns of senior citizens and the impact high concentrations of older Americans place on local service organizations and medical programs. There are parts of the our nation, such as Pinellas County, Florida which I represent, and other areas throughout the Sunbelt with high concentrations of senior citizens who give us an advance look at what the demographic makeup of our entire nation's population will be over the next 20 years as the general population ages. Do you see a benefit to a supplemental project that would provide a larger sampling of an area or areas of our nation which currently have large concentrations of older Americans to provide more specific and reliable information about their needs and characteristics? How much would be needed to undertake this project?

Dr. Williams. Florida is most certainly a bellwether state that can give us an advance demographic and economic look at what might happen when the nation's population ages dramatically over the next twenty years. It is also clear that inadequate scientific attention has been given to the impact of retirement on areas of the sunbelt that have very high proportions of older people. The Health and Retirement Survey as currently planned will almost certainly include information on the migration plans of those planning to move to Florida, and so will be useful for planning and policy analysis in Florida. The survey is likely to include a sample, depending on the final sample size allowed by the budget, of about 600-800 Floridians. St. Petersburg is likely to be represented within any Florida sample. Further, the number of study respondents actually residing in Florida will probably double over five to eight years as survey respondents migrate to Florida. This number will be adequate for a number of important research and planning purposes. However, the sample size, under current budget estimates, will not be adequate for a number of other state and local analyses.

Enhancements and supplemental studies could be worthwhile from both a policy and scientific perspective. First, it would be valuable to over sample some of the areas from which retirement migrants move to sunbelt areas such as Florida. This would allow for a more accurate tracking and forecasting of retirement-related migration. Knowing the numbers and characteristics of future residents would undoubtedly be useful to states such as Florida. Such data would be very useful for exploring the impact of retirees on local service organizations and medical programs. Second, since the retirement process is likely to be different in areas with already high concentrations and densities of older people there is also good reason to over sample study respondents in these areas. The exact age range that the study encompasses will be decided during the design phase, but is likely to be in age range from 55-62 or 50-65. Unfortunately, without additional funds, the basic study could not accomplish the worthwhile over sampling described in the above two points.

Additionally, beyond the over sampling referred to in the above paragraph there is also a good rationale for conducting additional supplemental studies of the older populations in states or areas with high densities of older persons such as Florida, Arizona, and some parts of California. These more specialized studies could provide increased geographical coverage and provide a more detailed analysis of the impact of retirement migration on some local areas. Such studies could not be used, however, to study the bulk of retirement migration.

USE OF ANIMALS IN ALZHEIMER'S RESEARCH

Mr. Weber. Do animals play an important role in ~~AD~~ Alzheimer's research?

Dr. Williams. Since the living human brain is not available for biochemical study, the study of Alzheimer's disease (AD) has relied heavily on autopsy tissue and animal studies. Since AD is a disease of age, it has been important to have aged animals for study. Old rats do not develop AD, but they do show cholinergic and behavioral deficits that are a useful model for AD. Furthermore, surgical and other brain lesions in rats have proved to be of great value in elucidating the type of neurodegeneration that occurs in AD. Although non-human primates, dogs, and bears develop brain pathology that resembles AD, these animals are not commonly used in AD research. Laboratory animals are essential for the elucidation of the functional anatomy, biochemistry, pharmacology, and molecular biology of normal brain. The development of a good laboratory animal model for AD would accelerate AD research considerably, but this has so far eluded researchers.

Mr. Weber. What is the likelihood that significant progress in Alzheimer's research could be made without animals?

Dr. Williams Without the use of research animals, AD research would be confined to the examination of post-mortem human tissue. The likelihood that such studies alone would lead to the discovery of the cause, prevention, or treatment of AD is extremely remote. It has been possible to carry out the initial research on nerve growth factor, a potential treatment for AD, in rodents; it is now necessary to expand this research to primates before testing in humans.

RURAL HEALTH AND AGING CENTERS

Mr. Weber. How is the Institute progressing in its selection of a facility for the Center for Studies of Older Rural Populations?

Dr. Williams. In December, 1989, the NIA issued a Request for Applications for "Exploratory Center Grants on the Health and Effective Functioning of Older Rural Populations." These centers will establish coordinated, multidisciplinary research environments on the social, economic, psychological, environmental, and biomedical factors affecting the aging processes and the health and effective functioning of older people in rural areas. An emphasis has been placed on five general research issues, including the changing socio-demographic and epidemiologic characteristics of older rural populations, the occupational and physiochemical environment, the population aging of rural communities, the availability, utilization, and quality of health-care and other social services, and aging rural people as resources.

Since the receipt date for applications was March 20, 1990, we do not yet know how many applications were actually submitted. However, NIA received about 25 letters of intent to submit an application and about twice as many inquiries, indicating the strong interest in this topic. Once the applications are received, we

will proceed with the scientific merit review and the selection of two applicants for funding in FY 1990.

Mr. Weber. What are some of the criteria the Institute is considering in selecting a facility?

Dr. Williams. Primary consideration will be given to each applicant's scientific merit: its overall program goals and the development of a well-defined central focus of clear importance and relevance to the goals and mission of the NIA, its potential to develop research programs of high merit as evidenced by previous scientific accomplishments, and its access to rural populations. Additional consideration will be given to administrative factors, such as the appropriateness and adequacy of the multidisciplinary teams constituting the Center's members, of internal communication and cooperation among the investigators involved in the Center, management, that is, fiscal administration, procurement, property, personnel, mechanisms for reviewing the use of and administration of funds, etc.

Mr. Weber. I understand that the research conducted at this center may provide benefits not only for the elderly, but for the population as a whole. Could you elaborate on this?

Dr. Williams. Many of the research issues covered by the Centers are of concern to more than just older people. The changing socio-demographic and economic characteristics of rural areas affects all age groups through its impact on the availability of health-care and other social services. For example, research on transportation problems and the delivery of health-care in remote areas will provide information that could benefit younger as well as older people. Similarly, research on the occupational and physiochemical environment, in terms of its impact upon health and functioning, will be relevant to all age groups.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

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NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

For carrying out section 301 and Title IV of the Public Health Service Act with respect to aging [$243,509,000] *$248,938,000.*

(Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriation Act, 1990.)

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Amounts Available for Obligation 1/

	1989 Actual	1990 Appropriation	1991 Estimate
Appropriation	$225,578,000	$243,509,000	$248,938,000
Enacted administrative reduction	-2,935,000	-824,000	---
Sequester Order	---	-3,230,000	---
Subtotal, adjusted appropriation	222,643,000	239,455,000	248,938,000
Real transfer to the Office of the Assistant Secretary for AIDS research for AZT	-4,000	---	---
Comparative transfers to:			
Fogarty Internationl Center, NIH for passport activities	-3,000	-3,000	---
Division of Research Resources, NIH for administrative cost of RCMI Program	-7,000	---	---
Comparative transfer from:			
Office of the Director, NIH for FTE increase	+259,000	---	---
Subtotal, adjusted budget authority	222,888,000	239,452,000	248,938,000
Unobligated balance lapsing	-94,000	---	---
Total, obligations	222,794,000	239,452,000	248,938,000

1/Excludes the following amounts for reimbursable activities carried out under this account: 1989 -- $1,506,000; 1990 -- $2,000,000; 1991 -- $2,000,000.

Excludes $2,000 for royalties received in 1989.

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Budget Mechanism

(Dollars in Thousands)

	1989 Actual		1990 Appropriation 1/		1991 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research grants						
Research projects:						
Noncompeting	431	$92,026	450	$103,433	453	$106,169
Admin. suppl	(24)	1,200	(22)	1,308	(22)	1,325
Competing						
Renewal	50	14,911	43	14,735	43	16,725
New	137	23,541	108	19,668	105	21,576
Supplemental	7	496	5	553	5	590
Subtotal, competing	194	38,948	156	34,956	153	38,891
Subtotal, res. proj	625	132,174	606	139,697	606	146,385
Research Centers						
Spec./comp. ctrs	18	22,953	24	26,517	24	26,517
Other research						
Res. career program	106	6,785	91	7,138	91	7,138
Minority biom. res		446		455		494
Other res. related	28	1,719	31	1,646	31	1,646
Subtotal, other res	134	8,950	122	9,239	122	9,278
Total, research grants	777	164,077	752	175,453	752	182,180

Training						
Individual awards:						
Noncompeting	19	495	17	436	21	538
Competing						
Renewal						
New	13	336	14	351	10	249
Subtotal, individual	32	831	31	787	31	787
Institutional awards:						
Noncompeting	275	5,749	292	7,180	314	7,737
Competing						
Renewal	33	824	26	652	16	398
New	47	1,227	36	901	24	598
Subtotal, institutional	355	7,800	354	8,733	354	8,733
Total, training	387	8,631	385	9,520	385	9,520
Research & development contracts	40 FTEs	12,806	36 FTEs	11,920	36 FTEs	11,920
Intramural Research	244	25,639	243	28,292	250	30,558
Research management and support	112	11,735	126	13,751	131	14,760
Extramural Construction		0		516		0
Total	356	222,888	369	239,452	381	248,938
HIV/AIDS	(3)	(502)	(5)	(859)	(5)	(929)

1/Includes approximately $516,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

CROSSWALK - 1989 Actual
(Dollars in thousands)

PROGRAM ACTIVITY	MECHANISM								
	Research Grants			Training Programs		Research and Devel. Contracts	Intramural Research	Res. Mgmt. and Support	Total
	Research Projects	Research Centers	Other Research	Indiv.	Instit.				
Aging	$132,174	$22,953	$8,950	$831	$7,800	$12,806	---	---	$185,514
Intramural research	---	---	---	---	---	---	$25,639	---	25,639
Research management and support	---	---	---	---	---	---	---	$11,735	11,735
Total	132,174	22,953	8,950	831	7,800	12,806	25,639	11,735	222,888

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National Institute on Aging

CROSSWSWALK - 1990 Appropriation_1/
(Dollars in thousands)

PROGRAM ACTIVITY	MECHANISM								
	Research Grants			Training Programs		Research and Devel. Contracts	Intramural Research	Res. Mgmt. and Support	Extramural Construction
	Research Projects	Research Centers	Other Research	Indiv.	Instit.				
Aging	$139,697	$26,517	$9,239	$787	$8,733	$11,920	---	---	---
Intramural research	---	---	---	---	---	---	$28,292	---	---
Research management and support	---	---	---	---	---	---	---	$13,751	---
Extramural Construction	---	---	---	---	---	---	---	---	$516
Total	139,697	26,517	9,239	787	8,733	11,920	28,292	13,751	516

_1/Includes approximately $516,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

CROSSWALK - 1991 Estimate
(Dollars in thousands)

PROGRAM ACTIVITY	MECHANISM								
	Research Grants			Training Programs		Research and Devel. Contracts	Intramural Research	Res. Mgmt. and Support	Total
	Research Projects	Research Centers	Other Research	Indiv.	Instit.				
Aging	$146,385	$26,517	$9,278	$787	$8,733	$11,920	---	---	$203,620
Intramural research	---	---	---	---	---	---	$30,558	---	30,558
Research management and support	---	---	---	---	---	---	---	14,760	14,760
Total	146,385	26,517	9,278	787	8,733	11,920	30,558	14,760	248,938

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Summary of Changes

1990 Estimated budget authority	$239,452,000
1991 Estimated budget authority	248,938,000
Net change	+9,486,000

Changes:	1990 Current Estimate Base Pos. (FTEs)	1990 Current Estimate Base Budget Authority	Change from Base Pos. (FTEs)	Change from Base Budget Authority
A. Built-in:				
1. Annualization of January 1990 pay raise		$19,157,000		+230,000
2. Within-in grade increases		19,157,000		+541,000
3. One extra day of pay		19,157,000		+49,000
4. January 1991 payraise		19,157,000		+658,000
5. Federal Employees Compensation Fund increase		68,000		+2,000
6. Unemployment Compensation increase		32,000		+1,000
7. Payment for centrally furnished services		6,001,000		+798,000
8. Increase for service and supply fund		2,861,000		+98,000
9. DHHS Working Capital Fund		231,000		-11,000
10. Federal Telecommunications System (FTS) increase		126,000		+5,000
11. Increased cost of laboratory materials and other supplies		16,885,000		+459,000
Subtotal				+2,830,000
	No.	**Amount**	**No.**	**Amount**
B. Program:				
1. Research project grants:				
a. Noncompeting	450	104,741,000	+3	+2,753,000
b. Competing	156	34,956,000	-3	+3,935,000
Total	606	139,697,000	0	+6,688,000
2. Other research		9,239,000		+39,000

Summary of Changes - Continued

	FTEs	Amount	FTEs	Amount
3. Intramural Research.....	243	13,444,000	+7	+245,000
4. Research Manangement and Support.....	126	5,713,000	+5	+200,000
5. Extramural Construction.....		516,000		-516,000
Subtotal.....			+12	+6,656,000
Total, changes.....				+9,486,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Budget Authority by Activity

(Dollars in thousands)

	1989 Actual		1990 Appropriation 1/		1991 Estimate	
	FTEs	Amount	FTEs	Amount	FTEs	Amount
Aging	---	$185,514	---	$196,893	---	$203,620
Intramural	244	25,639	243	28,292	250	30,558
Research Management and Support	112	11,641	126	13,751	131	14,760
Extramural Construction	---	---	---	516	---	---
Total, obligations	356	222,794	369	239,452	381	248,938
Unobligated balance lapsing	---	94	---	---	---	---
Total, Budget Authority	356	222,888	369	239,452	381	248,938
HIV/AIDS	(3)	(502)	(5)	(859)	(5)	(929)

1/Includes approximately $516,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

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National Institute on Aging

Budget Authority by Object

	1990 Appropriation	1991 Estimate	Increase or Decrease
Total number of full-time permanent positions	292	299	+7
Total compensable workyears:			
Full-time employment	400	412	+12
Full-time equivalent of overtime and holiday hours	6	6	---
Average ES salary	$78,400	$95,100	+16,700
Average GM/GS grade	11.5	11.5	---
Average GM/GS salary	$33,875	$35,061	+1,186
Average salary, grades established by act of July 1, 1944 (42 U.S.C.207)	$68,547	$70,946	+2,399
Average salary of ungraded positions	$39,727	$41,117	+1,390
Personnel compensation:			
Full-time Permanent	$11,097,000	$11,517,000	+420,000
Other than full-time permanent	3,754,000	3,914,000	+160,000
Other personnel compensation	693,000	752,000	+59,000
Special personnel service payments	830,000	899,000	+69,000
Total, personnel compensation	16,374,000	17,082,000	+708,000
Personnel benefits	2,783,000	2,989,000	+206,000
Benefits for former personnel	12,000	12,000	---
Travel and transportation of persons	485,000	509,000	+24,000
Transportation of things	104,000	109,000	+5,000

	1990 Appropriation	1991 Estimate	Increase or Decrease
Rent, communications, and utilities.	1,926,000	2,022,000	+96,000
Printing and reproduction.....	344,000	361,000	+17,000
Other Services:			
Project contracts.....	11,920,000	11,920,000	---
Centrally furnished services.....	5,866,000	6,604,000	+738,000
Standard level user's charge	135,000	195,000	+60,000
Other.....	8,977,000	9,597,000	+839,000
Supplies and materials.....	2,624,000	2,755,000	+131,000
Equipment.....	2,936,000	3,083,000	+147,000
Grants, subsidies, & contributions..	184,966,000	191,700,000	+6,734,000
Total budget authority.....	239,452,000	248,938,000	+9,486,000

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NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Significant Items in House and Senate Appropriation Committee Reports

Item	Action Taken or to be Taken
1990 House Report	
1. "The Committee considers Alzheimer's disease to be one of the most important health problems facing this country. It is the intention of the Committee that the majority of funds added by the Committee be used to expand Alzheimer's research. These funds should allow the Institute (NIA) to expand the National Alzheimer's Education Program and its program of caregiver education, to initiate additional State Alzheimer's Education Program demonstration projects, to increase research on special older populations such as the oldest old and rural and minority elderly, and to support additional Alzheimer's Disease projects." (p. 69)	The NIA continues to place high priority on funding Alzheimer's disease, including understanding its cause(s), properly diagnosing the disease, developing new treatment and management strategies, and educating both the lay and professional audience with regard to the disease. There are two major components to NIA's AD educational efforts, one being the Alzheimer's Disease Education and Referral Center which NIA will fund to the full extent possible within available funds. The second component is the Alzheimer's Disease Research Centers program which provide training to both lay and professional audiences through their educational core. The NIA will also expand its research efforts with respect to special populations. Initiatives have been developed to expand studies of minority elderly; specifically, all program announcements and requests for applications require that applicants include minority elderly in their research protocols where appropriate. NIA will award two rural health care centers in FY 1990 to examine the health needs of this under served population, including minority elderly and the oldest old.

Item	Action Taken or to be Taken
1990 Senate Report	
1. "The tragedy of Alzheimer's disease (AD) is one of growing proportion with potentially devastating public health consequences. The Committee is, therefore, encouraged that research on AD continues to be a high priority of the NIA....The Committee feels that because of the high incidence of Alzheimer's and with the aging trends of the American population all but guaranteeing that the problem will increase in magnitude, additional research is urgently needed." (p. 144-145)	The NIA continues to place the highest priority on funding projects directed at finding the cause(s) of AD, diagnosing it and finding new treatment and management strategies to cope with the disease. In keeping with the suggestion from the Senate, NIA will direct a major portion of the increased funding provided to research on AD.
2. "The Committee is also supportive of projects which serve as catalysts for collaboration between scientists, service providers, and affected individuals and families. Of particular interest are statewide collaborative models which link information dissemination and education for professionals and families data gathering and analysis, autopsy network development and tissue study coordination, and clinical outreach. The Institute is encouraged to incorporate such core projects within the additional funds available for Alzheimer's research." (p. 145)	When the Alzheimer's Disease Research Centers were established, there were a number of major components that were deemed to be important for their success. These included information dissemination and educational activities for both families and caregivers; supplemental funding was provided to each center in both FY 1988 and FY 1989 to carry out such activities. Other critical elements are autopsy and tissue banking which are components of most of the centers; these are important for conducting genetic studies and for confirming diagnosis of AD. All centers have a clinical outreach component. These elements will continue to be funded in FY 1990 and FY 1991 and expanded to the extent of satellite research centers.

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Item	Action Taken or to be Taken
3. "The Committee continues to be very supportive of collaborative efforts by the NIA and the Agency for International Development (AID) to address the ever growing health problems of the aged throughout the world....Accordingly, the Committee again urges NIA to develop collaborative projects with AID, and further, also continues to be most supportive of NIA's efforts to establish a Pacific basin and Southeast Asia international gerontology focus in Hawaii." (p. 147)	The NIA continues to work with AID to develop collaborative projects to develop a data base on the 85 plus population throughout the world and to establish the level of care required by this age group as compared to that in the U.S. NIA has taken steps to establish a field station in Hawaii in FY 1990 to coordinate efforts to initiate and conduct comparative epidemiological research projects related to conditions of aging populations in Hawaii, the Pacific, and Asia.
4. "The Committee continues to stress the importance of training more academic leaders and educators in all aspects of aging research and geriatrics through such mechanisms as the newly initiated geriatric research and training centers (GRTC)..." (P. 147)	The NIA, following the recommendations of the Institute of Medicine, has established a program of training through the Claude D. Pepper Geriatric Research and Training Centers. One such center was established in FY 1989 with another to be funded in FY 1990. In addition, other geriatric training efforts will be carried out through the Geriatric Career Award Program and through the Geriatric Research Institutional Training award program. Funding for these programs is expected to be initiated in FY 1990.
5. "In order to assist people in continuing whatever lifestyle they want, including the opportunity to continue working, the Committee urges within available funding renewing the longitudinal health and retirement history survey to have better knowledge and information on the impact of health and retirement practices of older people." (p. 148)	NIA plans to fund a cooperative agreement in FY 1990 to examine the social, health, and economic implications of the rapidly aging population with respect to retirement decisions.

Item	Action Taken or to be Taken
6. "The Committee again urges NIA to support pre- and post-doctoral research fellowship awards for qualified nurses. The Committee is pleased to learn of NIA's coordinated efforts with the National Center for Nursing Research, the National Institute of Mental Health, and the National Center for Health Services Research to establish a vigorous research and training initiative on the subject of caregiver burdens related to care of family members with Alzheimer's disease and other dementias, and how these burdens may be eased. Further, the Committee strongly recommends the continuation of the Teaching Nursing Home Program, which links nursing and medical schools to nursing homes. NIA is urged to continue to utilize nursing knowledge and expertise in its activities and programs." (p. 148)	The NIA continues to encourage and support qualified nurses in training programs related to aging. Additionally, the education core component of the Alzheimer's Disease Research Centers provides training for all allied health professionals, including nurses, with respect to the burdens of care for Alzheimer's patients. The NIA also cosponsors with the National Center for Nursing Research (NCNR) projects directed at understanding the burdens of care in AD. This is one of the many ways in which NIA collaborates with NCNR, others being the long-term care and frailty initiatives. The Teaching Nursing Home program has long been a strong component of NIA's research agenda and will continue to be supported.

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1990 Amt. Authorized	1990 Appropriation	1991 Amt. Authorized	1991 Budget Estimate
Research and Investigation.....	Section 301	42§241	Indefinite	$229,932,000	Indefinite	$239,418,000
National Institute on Aging.....	Title IV, Part C	42§289k-2 - 289k-5	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	42§288	Such sums as necessary 1/	9,520,000	Authorizing legislation to be requested 1/	9,520,000
Total Budget Authority.....				239,452,000		248,938,000

1/This training authority is shared with other research training programs of the National Institutes of Health; the Alchohol, Drug Abuse, and Mental Health Administration.

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Appropriations History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1981	74,441,000	75,493,000	75,469,000	75,608,000
1982	74,084,000 1/	86,059,000	85,591,000	81,903,000
1983	84,556,000	96,104,000	91,887,000	93,993,000
1984	99,408,000	112,516,000 2/	112,084,000 2/	115,720,000
1985	117,390,000	140,102,000 3/	144,799,000	144,862,000
1986	135,376,000	149,067,000 4/	156,618,000	156,491,000
1986 Sequester				-6,729,999
1987	145,829,000	174,279,000	179,582,000	177,681,000
1988	156,174,000	203,411,000 5/	199,642,000	194,746,000
1989	204,770,000	225,578,000	210,222,000	222,642,000
1990	229,620,000 6/	241,528,000	245,490,000	242,685,000 7/
1990 Sequester				-3,230,000
1991	248,938,000			

1/ Reflects the September Amendment; the original request was $84,186,000
2/ Excludes $2,168,000 in NRSA training programs not considered.
3/ Excludes $3,069,000 in NRSA training programs not considered.
4/ Excludes $4,642,000 in NRSA training programs not considered.
5/ House Allowance consolidated all AIDS activities in OASH.
6/ The 1990 request excludes funds for the National HIV program ($870,000) proposed for consolidation in the Office of the Assistant Secretary for Health.
7/ Excludes enacted administrative reduction of $824,000.

Justification

National Institute on Aging

	FY 1990 Appropriation		FY 1991 Estimate		Increase or Decrease	
	FTEs	BA	FTEs	BA	FTEs	BA
TOTAL....	369	$239,452,000	381	$248,938,000	+12	+$9,486,000
HIV/AIDS.	(5)	(859,000)	(5)	(929,000)	--	(+70,000)

General Statement

Aging research is entering an unprecedented era of challenges and opportunities. The National Institute on Aging (NIA) was established to conduct and support biomedical, social, behavioral, and neuropsychological research. In order to accomplish these goals, scientists at or supported by NIA direct their research toward a more complete understanding of the normal changes associated with aging, the diseases and disorders that occur later in life and the social and policy changes influencing the quality of aging. Simultaneously, the Institute supports applied research efforts leading to interventions that have the potential to prevent diseases and disorders and to promote effective functioning and independence in the older population.

As the population of the United States ages, policy decisions concerning health care and education will have to be made. The increase in size of the oldest segment of the population, those 80 years of age and above, is anticipated to rise to 30 percent of our total older population (65 years and above) by the year 2005. Recent studies reveal that approximately 40% of the over 85 population today require some daily assistance from family, friends or caregivers. These statistics portray a potential need for better health care and more social service systems.

NIA continues to stress the importance of basic research including fundamental studies of biological processes, the interaction of aging and diseases of aging, and biomedical and psychosocial factors in maintaining health and effective functioning in the middle and later years. Recognizing that no single process explains multiple and interacting changes that occur with age, the National Institute on Aging implements research programs that identify promising clues to many of the biomedical, behavioral and social changes associated with age. The Institute recognizes it's role as a leader in aging research by supporting an active training and career development effort.

Investigating Alzheimer's disease remains one of the NIA's highest priorities. This year much exciting progress has been made, including the possibility for a single, objective diagnostic test and the new possibilities for nerve growth factor to serve as an effective

intervention. Some research has focused on the possibility that the risk of Alzheimer's disease might be increased by age-related changes in healthy brain. New research initiatives for the future year include increased efforts to direct attention toward developing and testing behavioral, social, and environmental interventions for reducing the burdens of care, and evaluating the utility of special Alzheimer units in day care and long-term care settings.

Currently, the NIA is seeking to stimulate both biomedical and behavioral sciences research on gender and to improve minority health. Understanding basic characteristics of aging, promotion of health and effective functioning, and improving the quality of health services are other areas of concern to NIA.

Overall Budget Policy

The FY 1991 total budget request for the National Institute on Aging (NIA) stresses basic research, and totals $248,938,000, an increase of $9,486,000 over the 1990 estimate of $239,452,000. The FY 1991 request includes $929,000 for AIDS research.

In 1991, the request will support 453 noncompeting research project grants and 153 competing research project grants at a total funding level of $146,385,000. To accomplish these levels, NIA will negotiate down noncompeting awards by 10.5 percent and competing awards by 10.8 percent.

The FY 1991 request includes funding for 24 research centers. The request will support all ongoing research centers, including the Alzheimer's Disease Research Centers, two Claude D. Pepper Geriatric Research and Training Centers and two rural health care centers. All center awards will, however, be negotiated down by approximately 27 percent. The Other Research category will be maintained at approximately the same levels as in the FY 1990 current estimates. The total number of trainees supported in FY 1991 will be at the same levels as in the FY 1990 current estimates. The request will also fund 36 R&D contracts for $11,920,000.

The 1991 budget request for Intramural Research is $30,558,000, an increase of $2,266,000 over the 1990 current estimate of $28,292,000. The request for Research Management and Support is $14,760,000, an increase of $1,009,000 over the 1990 current estimate of $13,751,000.

Program Accomplishments

Alzheimer's Disease

Since the mid 1970's, research on Alzheimer's disease (AD) has become a high priority for the Nation. As it has become increasingly apparent that "senility" is not a normal part of aging, investigators from many fields of science have begun to study what causes this disease, and how it can be diagnosed, treated, and perhaps someday, cured. Although exact numbers are not known, it is estimated that almost 4 million people have AD. At present there are no established effective means of prevention or treatment. The burdens and costs of care are already enormous--$80 billion or more per year; and within the growing number of old and very old persons susceptible to this disease, the numbers affected and the associated costs will reach catastrophic proportions early in the next century.

The search for the cause of Alzheimer's disease has focused on the role of genes, toxins, infectious agents, head trauma, stress, and changes in the immune system, the endocrine system, and normal metabolic processes. Scientists are looking at each of these as possible leads to what causes of Alzheimer's disease, either alone or in combination. Others are exploring the possibility that the risk of Alzheimer's disease might be increased by age-related changes in healthy brain. Research achievements during the past year continue to bring us closer to these goals.

Recent data from a community-based epidemiological study in East Boston indicates that AD may be more prevalent than previously reported. It is now estimated that about 10 percent of persons over 65 have AD, with nearly half, 47 percent, of these over age 85 showing some degree of AD-related cognitive decline. If extrapolated to the entire U.S. population, there may be as many as 5 million persons with AD by the end of this century.

The neuritic plaques that are among the major hallmarks of AD contain dense insoluble deposits of amyloid protein and fragments of nerve cells. Several laboratories have shown that the principal component of the plaque amyloid of AD and of vascular amyloid is the same small protein (amyloid beta-protein). It recently has been demonstrated that protein is present in non-neuronal tissues (including skin, subcutaneous tissue, and intestine) and blood vessels of AD patients as well as in a small proportion of normal old people. Until these findings, the amyloid beta-protein was found only in the brain. Thus, these data suggest that AD may be a widespread systemic disorder and support other findings indicative of a metabolic defect in AD.

The function of the amyloid beta-protein in normal or in AD brains is not known. It is part of a larger protein molecule (amyloid precursor protein, APP) that normally spans the nerve cell membrane. Recently, a synthetic peptide constructed of the first 28 amino acids of the amyloid protein has been synthesized and placed into a nerve cell tissue culture system. In the presence of this peptide, the nerve cells stayed alive longer than did untreated cells. These results indicate that portions of

the amyloid protein can have a growth enhancing effect on nerve cells. Other scientists stimulated cells to release a peptide consisting of about the first 105 amino acids of the amyloid protein. This peptide had a toxic effect upon neighboring cells in culture. Thus, abnormal processing of the APP could be a consequence of AD and produce some of the cellular events associated with this disease.

Aging may increase susceptibility of the nervous system to toxins and other environmental perturbations. The role of neurotoxins, both from the environment as well as within the brain, in causing specific cells to die is an area of much scientific interest. Preliminary evidence has emerged that AD may be caused by an infectious agent. This finding resulted from researchers successfully transmitting a blood-borne infectious substance from humans at high risk of developing AD to laboratory animals. The agent, which results in a fatal brain disorder, produces brain pathology similar to that caused by Creutzfeldt-Jacob disease, a rare and progressive brain disease. The success of this study is believed to be based on the greater amount of the transmissible agent at the early or pre-clinical as opposed to end stages of disease. Confirmation and additional research will be necessary before we know for sure whether some cases of AD have an infectious origin. A multi-center replicative trial is now under consideration.

Molecular genetic studies on AD have resulted in new research findings. Previously it had been reported that a region on chromosome 21 is associated with familial AD and is near that responsible for production of the amyloid protein which is found in the Alzheimer brain. It is now believed that AD may involve more than one gene: in some cases the gene might be located on chromosome 21, in other cases other chromosomes may be involved. The NIA is now supporting an AD DNA repository which will make available to qualified investigators, material from well characterized patients and controls for molecular genetic studies.

During development, the brain has the capacity to reorganize itself in response to changes in sensory input and following injury due to trauma or disease. This capacity, termed plasticity, seems to be diminished in older individuals. If plasticity can be stimulated using drugs or other factors, there is hope that lost brain function can be partially reinstated.

Research is now finding ways to treat brain injury by stimulating the brain to heal itself. Since AD causes massive brain injury, such work has important implications for developing treatments. In one study, research on nerve growth factor (NGF), a peptide and one of several known trophic factors that works specifically on nerve cells, has demonstrated that NGF can influence the survival of a particular group of brain cells (the cholinergic cells) following injury. NGF or similar substances may someday be used to prevent cell loss in Alzheimer's and other degenerative diseases, where specific populations of brain cells are targeted for destruction. A major conference on the "Molecular and Cellular Mechanisms of Neuronal Plasticity in Aging and Alzheimer's Disease" was held addressing these issues.

Interim analyses in 1989 from a multi-center clinical trial study on the safety and efficacy of tetrahydroaminoacridine (THA), an experimental drug which may help control memory loss in some patients with AD, indicated the necessity to continue the study in order to ascertain whether it is clearly beneficial and safe. THA is one of several drugs being tested as a treatment for Alzheimer patients.

The NIA is intensifying its efforts to develop a focused research program on social and behavioral aspects of AD with a special emphasis on burden of care. Topics of concern include: caregiver's perceptions of and responses to AD symptoms; the nature of the impact on caregivers; patterns of health care for AD victims and their families; interventions for reducing the burdens of care; and forecasting of future long-term care needs and costs.

Understanding Aging

Success with invertebrate systems has suggested that it may be possible to identify potential longevity assurance genes in mammals as well. Long-lived Drosophila have been isolated by selection for delayed fecundity, and a long-lived nematode mutant was isolated after mutagenesis and selection for increased life span. Thus, both mutagenesis and natural selection have been successful in isolating individual organisms with extended life span. It is hoped this will lead to identification of some longevity assurance genes in these species, as some promising clues have already been uncovered. For example, the long-lived flies are more resistant to desiccation, alcohol, and starvation; however, only starvation resistance co-varies with life span. The long-lived flies also contain increased levels of a more active variant of superoxide dismutase. The question remains as to whether selection will work in mice, or in other mammals. The mouse is a very useful and practical animal model and success in this species would further the cause of identifying longevity assurance genes in humans. Successful identification of these genes in humans will provide a basis for effective intervention.

Progress is being made towards identifying proteins, messenger RNAs, and other signals of aging, which form the basis for the limited life span of cells. These substances are responsible for the control of cell growth and development and understanding how cells age. Age-related changes in gene expression have been shown to occur at the level of translation and/or RNA processing. Although senescent cells appear to transcribe the genes for ornithine decarboxylase and fibronectin normally, only low amounts of protein are made. Furthermore, whereas the cellular oncogene c-myc is transcribed, the transcript is not processed into active messenger RNA. These results suggest that transcription rates are only one level for control of gene expression in senescent cells, and confirm the need to look for senescence-related changes at all levels of gene expression.

Continuing research is showing that advancing age is accompanied by changes in immune function that make older individuals more vulnerable to disease. NIA-supported research has recently discovered important information about the nature of these age-related changes--that aging immune system is made up of responding and nonresponding immune cells

rather than partially responding cells, as previously believed. It is anticipated that the results of this and other NIA-supported studies might ultimately lead to treatments that might halt or reverse the immunosenescence process (the aging of the immune system), thus improving the quality of life for older people through better health. An example is the discovery of NIA-funded research that intravenous administration of recombinant interleukin 2 can stimulate the immune response in childhood cases of severe combined immune deficiency sufficiently to prevent serious infections. This suggests that similar intervention may be effective in slowing the age-related decline in immune function in older people, thereby decreasing the vulnerability of these people to infectious disease.

Low calorie diets fed to mice and rats in a nonmalnutritional way greatly extend the maximum life span, decrease the incidence and/or delay the onset of cancer and other late life diseases, and retard the rates of change for most age-sensitive biologic measures tested to date. Present research is focused on the mechanisms which underlie the actions of caloric restriction in rodents as well as the possibility that aging is retarded in primates fed low calorie diets. Recent studies suggest that cellular damage, probably caused by free radicals (highly reactive metabolic by-products), is reduced in animals fed low calorie diets. The reduction in damage may be due to an increased activity of enzymes (catalase, superoxide dismutase) which inactivate free radicals.

Disorders of sleep afflict over half of the people 65 and older who live at home and about two-thirds of those who live in long-term care facilities. Problems of nighttime wakefulness and daytime sleep disrupt not only the older persons' lives but also those of their families and caregivers. It is not known whether these disorders reflect underlying pathologies or the normal maturation of the aging nervous system, or whether the psychosocial and environmental conditions of the aging person contribute to these changes. Recent work indicates that exposure to bright light, such as early morning sunlight, for several hours on each of three days can readjust the sleep-wake cycles of older persons as well as those travellers suffering jet-lag and possibly those persons on shift-work. In order to further the development of therapeutic strategies for these disorders, the NIA has taken the lead in sponsoring an NIH "Consensus Development Conference on the Treatment of Sleep Disorders of Older People."

Promoting Health and Effective Functioning

Research is now documenting medical, social, and behavioral risk factors for morbidity and mortality in old age, identifying previously neglected health concerns and behavioral and medical problems in community-dwelling older people, and evaluating the impact of socio-behavioral, medical, and environmental interventions on the health, effective functioning, and well being of older individuals. For example, a long-term follow-up from the Alameda County Study demonstrates the persistent influence even in very old age of behavioral and social factors (e.g., smoking, physical activity, social network participation, and lower socioeconomic position) on morbidity, functioning and mortality. The

identification of antecedents which influence such social and behavioral risk factors and their change over time and as people age, suggests pathways for interventions to sustain the vigor and independence of the middle years.

Persons over age 65 comprise 12 percent of the nation's population but consume over 30 percent of the prescription drugs dispensed. Older patients often take several medications for multiple disorders. Side effects and interactions of these drugs can interfere with proper treatment. NIA's geriatric pharmacology research program supports research to improve drug treatment for older persons. For example, research has documented a drug interaction which should improve prescribing practices. Nifedipine (used for treating hypertension) was shown to cause excessive drops in blood pressure in patients taking one anti-ulcer medication (cimetidine), but did not provoke these drops in pressure if another anti-ulcer drug (ranitidine) is used. Many older persons simultaneously take nifedipine (or similar drugs) and anti-ulcer medications. This finding should help to prevent blood pressure drops which can cause falls and fractures among older persons.

Other researchers have found that psychotropic drug use by older persons is associated with hip fractures due to falls, probably due to the effect of these drugs on balance; short-acting medications have been found to have considerably less risk than long-acting ones. Psychotropic drug prescribing for nursing home residents can often be safely reduced or adjusted. Hence testing an approach to prevent injurious falls by improving drug prescribing in nursing home populations appears warranted.

Urinary incontinence is a major problem and significant cause of disability and dependency among older persons. NIA-supported research analyzed the effectiveness of pelvic muscle exercises and biofeedback as a treatment for stress incontinence (incontinence provoked by coughing or straining, etc.). Results revealed a 54 percent reduction in symptoms using exercise alone, while exercise reinforced with biofeedback produced a 61 percent reduction in symptoms. In the exercise-plus-biofeedback group, 23 percent had a 100 percent reduction in symptoms, with another 49 percent reducing their number of urine losses by 50 percent and only 3 percent actually showing an increase in symptoms. Although these interventions have demonstrated that urinary incontinence can be eliminated or improved in a variety of populations and settings, follow-up studies also show that there are often problems with long-term maintenance, especially with residents in nursing homes. A cooperative agreement supported jointly by NIA and the National Center for Nursing Research is thus examining the effectiveness of staff management interventions to maintain long-term reductions in urinary incontinence.

These findings suggest important potential health cost savings. Surgery is widely used to treat stress incontinence. The estimated cost of these surgical procedures is approximately $4,000, including hospitalization, anesthesia and ancillary costs. Behavioral treatment for stress incontinence costs approximately $300 per patient. Approximately 200,000 women over the age of 60 suffer from pure stress incontinence. Assuming that only 23 percent of these (the percentage shown to have a 100 percent reduction in symptoms with exercise plus biofeedback) are cured by

behavioral treatment, associated potential savings in surgery-related costs could be approximately $170 million per year.

The extent to which habitual physical exercise can forestall or dampen age-associated physiologic decrements, inhibit the development of diseases and increase longevity are the topics of research supported by NIA. Accumulating evidence which suggests that the usually expected age-associated changes in several physiologic parameters (blood glucose tolerance, skeletal muscle strength, cardiac measures) occur to a lesser extent if at all in physically fit older persons. An NIA-supported epidemiologic study shows that staying physically fit is associated with a longer life. For both sexes, the very least fit showed much greater risks death than those of even moderate fitness levels. These trends remained after statistical adjustments for age, smoking, cholesterol level, systolic blood pressure and other variables. The primary benefit seems to be fewer deaths from heart disease and cancer.

Also critical for maintaining health and effective functioning is NIA's substantial program of research on intellectual and social-psychological processes. The importance of maintaining intact memory, reasoning, decision-making, and language throughout the later adult years needs little further justification. Yet declines in these processes have frequently been reported. NIA-supported researchers are now showing that such declines can be remediated by training--with training effects lasting up to seven years beyond the initial session. External influences-presented--also alter the size of observed age differences in these key intellectual processes. Interventions and analyses based on these results now form an important part of the initiatives on sense of control over the life course and on cognitive functioning and aging. Results from such basic research inform the NIA special initiatives on the oldest old, long-tern care, human factors and health attitudes and behaviors.

Frailty and Prevention of Injuries

A major obstacle to good health and effective functioning for older persons is physical frailty: impairments in strength, balance, mobility, and endurance. These account for a great share of geriatric long-term care needs and risk for injurious falls. Studies have identified specific syndromes of impaired muscle strength and coordination contributing to falls and mobility limitations. Recent findings suggest that many aspects of physical frailty appear to be treatable and/or preventible. For example, NIA-supported researchers in Boston showed that frail 90 year old nursing home residents could double their leg strength and walk better after an eight-week leg strengthening program. In addition, human factors research on the physical environment is showing how falls, automobile accidents, and other late life injuries can be prevented.

Other interventions also hold promise. In a three-year study involving women averaging 81 years old, researchers found that physical activity can slow the loss of bone mineral. Further follow-up of such studies is needed to determine the extent to which these approaches can prevent disabling hip fractures and other consequences of osteoporosis.

Many older persons have impaired balance which can lead to falls and hip fractures. One such study indicates that, in some older people, such impairment seen on an initial test may be much less apparent upon intervention and subsequent retesting. These results suggest that postural training holds promise as a way to reduce injurious falls in older persons.

Injuries are a leading cause of disability and death in old age. Falls, the major source of injury among older persons, are associated with hip fractures and long-term disabilities resulting in costly health care utilization and diminished quality of life. Diminished bone strength due to osteoporosis is a critical factor accounting for high fracture rates from falls among older persons. Falls are not, however, an inevitable consequence of aging and can often be prevented through medical, environmental and behavioral interventions.

Human factors is an approach to research that focuses on how human performance is limited or facilitated by the physical environment and structure of daily activities. In human factors research, for example, frailty is not considered solely a problem of the individual but as a problem of certain older adults interacting with particular environments where they are exposed to risk or to some hurdle. Meal preparation in a standard kitchen is a problem for many frail elderly adults (in one recent survey 30 per cent of all females 85 and over reported difficulty in meal preparation). An NIA-supported researcher is currently investigating the range of motion, types of grasp, physical strength, and sensory functioning demanded of adults by kitchen tasks and seeking to relate these findings to the capacities of a group of frail older adults. The immediate outcome is specific knowledge of the functional limitations of a frail elderly population. A likely secondary outcome is recommendations for modifying kitchen design that will facilitate the functioning of such a population.

The fastest growing segment of the driving population is over 75 years old and older drivers considered as a group have more accidents per mile driven than any other age group except the youngest drivers. Researchers in human factors and related fields are now addressing the related problems of how to assess and improve the driving performance of older adults and how to modify the driving environment (both the car and the highway) to make it elder friendly. Initial findings reveal widely disparate accident rates among different groups of older drivers, with the highest rates among those diagnosed as having Alzheimer's disease. These preliminary findings need to be substantiated on a larger scale before policy implications are drawn.

Long-Term Care

Long-term care issues are receiving increasing media attention, and public surveys have shown that the public-at-large is becoming increasingly aware of the financial and social implications of long-term care. Similarly, long-term care has become a topic of rapidly escalating concern to the Congress. Long-term care issues have been addressed in NIA appropriations report language since FY 1987, when House report language specifically provided funds for long-term care research on "the medical

and non-medical long term care needs of aged persons with chronic illness and their families."

Through a major initiative, the NIA is identifying research activities relevant to aging and long-term care. These activities focus on specific medical, social and behavioral aspects of institutional and noninstitutional care needs of the elderly population in general, including racial and ethnic minorities, rural and low income older people; and the oldest old; social and behavioral aspects of care for Alzheimer's disease patients and their caregivers. The concern for aging and long-term care research is reflected in all NIA grant and contract mechanisms; for example, all Centers programs (the NIA Teaching Nursing Home, the Alzheimer's Disease and Research Centers, the Geriatric Research and Training Centers, and the proposed centers for Rural Aging) include research relevant to long-term care. The National Long-Term Care Survey's 1989 wave is completed, and numerous researchers and other components of DHHS (including ASPE, HCFA, and NCHSR) have identified this survey as being urgently needed to understand key elements in long-term care and catastrophic health care costs, and have urged NIA to request Duke University to prepare a linked version of the database suitable for wide-spread usage.

Minority Aging and Health

Within the last year, the NIA has increased its efforts to expand the number and quality of projects focused on minority aging. The establishment of an NIA Work Group on Minority Aging lead to plans for a number of initiatives for increasing research on minority aging. These include the identification of several research priorities in the area which will serve as the focus for requests for research applications, increased opportunities for short and long term training of majority and minority investigators, and consideration of the re-establishment of a small grants program for support of pilot studies. In addition, the NIA is convening a Task Force on Minority Aging as a subcommittee of the National Advisory Council on Aging. This Task Force will be advisory to the NIA Director on minority aging issues overall, including identification of priority research issues, training issues and mechanisms of support. The Task Force will also serve as a link to the minority community and as a means of dissemination of information.

The NIA is also collaborating with the Administration on Aging, OHDS, HHS in support of a workshop on minority aging scheduled for February 1990 which is aimed at the development of research agendas in this area for the two agencies.

Training

Developing academic leadership in geriatrics is needed to train the increasing numbers of needed geriatric health personnel. This requires a continuum of support from the fellowship to the faculty level. NIA has developed a set of awards to support career development throughout this continuum. Research fellowship support is provided through individual and institutional training grants, as well as NIA's Complementary Training

Award, which supports the addition of trainees focused in aging to existing training grants in other disciplines. Career development at the junior faculty level is supported through NIA's Clinical Investigator Award, Academic Award, Physician Scientist Award, and NIA's new Geriatric Academic Program (GAP) award. NIA's Geriatric Leadership Academic Award supports established faculty in the development of research and training programs in aging.

To provide the needed environment for developing academic leadership in geriatrics, the Institute of Medicine recommended the establishment of centers of excellence in geriatrics. NIA has initiated the Claude D. Pepper Geriatric Research and Training Centers program and in FY 1989 made the first award to the University of Michigan.

Equally critical to fulfilling the NIA's mandate is the training of researchers in the biomedical, social, and behavioral sciences who will provide the basic science knowledge upon which future geriatric practice will be based. The NIA continues to support a wide range of training through the NRSA institutional pre- and post-doctoral programs and post-doctoral individual fellowships. The NIA has been particularly successful in expanding its support of training in the areas of demography and epidemiology. Given the multidisciplinary nature of research on aging, particular attention has been given to providing opportunities for scientists to obtain multidisciplinary training.

Research Resources

The NIA continues to provide needed resources to the scientific community by coordinating aging-related statistical data. Such data provides the crucial infrastructure for many NIA grants in such high priority areas as oldest old, long-term care, and productivity in work and retirement.

For several years, NIA has continued to support the widely used National Archive on Computerized Data on Aging which contains many and diverse studies on aging. More recently, NIA has funded such critically important data bases as the following: the National Longitudinal Study on Aging, the National Long Term Care Survey, the National Nursing Home Follow-Up Survey, the International Data Base on Aging, and the Established Populations for Epidemiological Studies of the Elderly.

A recently convened Ad Hoc Advisory Panel recommended that NIA take the lead in developing major new data collection in such areas as the processes and dynamics by which older persons move from functional independence to dependence, and retirement decisions and their consequences. Funds were provided for a new Retirement History Survey in FY 1990 and NIA is taking the necessary steps to implement this data base.

Animal resources continue to be a high priority of NIA, and we continue a sizeable commitment to establishing and maintaining colonies of aged animals. Plans are underway to establish a rodent colony for wide-spread usage of calorically-restricted animals. To date, caloric restriction has been the only intervention to be consistently effective in retarding age-related diseases or extending life span.

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A recent workshop, conducted by NIA on alternative models for research on aging, demonstrated that it is possible to gain an understanding of the mechanisms of aging through model systems not currently available. NIA thus proposes the development in the laboratory of some alternative model systems (from the commonly used rodent models) such as Peromyscus, Syrian hamsters or field studies of models such as opossum, lizards, or marine birds.

AIDS Research Program

The NIA AIDS Program

Since the beginning of the AIDS epidemic in the United States, approximately ten percent of AIDS cases have occurred among those aged fifty or more, a proportion that is expected to rise. In addition, significant numbers of older people may be already infected with the human immunodeficiency virus (HIV) but are not exhibiting disease symptoms.

Recent Research Accomplishments

Pathoimmunologic aspects of aging and infection with HIV have overlapping features. With advancing age, the immune system undergoes changes that are complex and variable, including increased incidence of infectious diseases and autoimmune disorders. The most significant aspect of immunosenescence is the decline in cell-mediated immunity, with T-cells the component of the immune system most sensitive to the aging process. Decline in cellular immunity is also characteristic of HI infection.

Recent advances in the AIDS program of NIA's intramural program shows promise for one suggested treatment of AIDS: the infusion of soluble CD4 receptor protein which binds the virus and prevents the interaction of HI and the cell. NIA scientists are also in the process of completing a study of the HI infection in older age groups where they examined various features of the immune system in these people as well as measured their response to the HI. This data suggest that older AIDS patients have more severe T-cell deficit than in younger groups.

Research Plans

Studies of HIV infection in people over 60 years of age will continue with special emphasis on the changes seen in certain T cell subsets in the peripheral circulation. In this age group there is a remarkable complete absence of a subset of toxic T lymphocytes which does not occur in younger patients. These cells play an important role in the defence against HIV and in the elimination of HIV infected tissue. The absence of the cells in the older AIDS patient may explain the decreased survival times seen in this group.

The work on the host interactions with the HIV will be expanded to define the function of the CD4 protein found in high concentrations in the blood of AIDS patients. The amount of CD4 protein in the blood of AIDS patients is about 10 times greater than that found in normal individuals and may influence the efficacy of the CD4 protein being given to AIDS patients.

Studies of the host-virus interactions will attempt to examine cell mediated immunity to the HIV both in HIV vaccine recipients and infected individuals. This will include determining the effects of the genetic shifts that the virus is capable of undergoing as these shifts relate to its ability to escape detection and destruction by the immune system.

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National Institute on Aging

Aging

Authorization: Indefinite

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$196,893,000	$203,620,000	+$6,727,000

Purpose and Method of Operation

The aging activity conducts and supports biomedical, behavioral and social research and training related to the aging process and the diseases and other special problems and needs of the aged. It consists of four major programs: Biomedical Research and Clinical Medicine; Behavioral and Social Research; Neuroscience and Neuropsychology; and Epidemiology, Demography, and Biometry.

Rationale for Budget Request

The FY 1991 budget request for Aging of $203,620,000 represents an increase of $6,727,000 over the FY 1990 current estimate. The Institute will support a total of 606 research project grants, approximately the same number as in FY 1990. In FY 1991, the Institute will support 24 research centers including 15 Alzheimer's Disease Research Centers two Claude D. Pepper Geriatric Research and Training Centers and two new rural health care centers.

During the upcoming fiscal year, the NIA will maintain its research efforts in such key priority areas as Alzheimer's disease; understanding the basic mechanisms and characteristics of aging; promotion of health and effective functioning in older individuals; and training and career development in geriatrics and aging research. Areas of increasing interest include research relevant to long-term care, studies of older rural populations, and AIDS-related research as it affects older people.

Biomedical Research and Clinical Medicine

This program is responsible for the planning, organization, and direction of programs of extramural research and training related to biological, clinical, and theoretical aspects of aging; the conceptualization of new research directions and projects in the aging field, the management and evaluation of grant applications and the dissemination of information to the scientific community, other Federal agencies, and the American public. Funding mechanisms used consist of research and training grant awards and research and development contracts.

One promising approach to characterizing longevity genes in humans is to selectively breed mice for increased life span, and then identify the genetic changes which have occurred to facilitate this increased life span. Any genetic changes which co-vary with life span may in fact contribute to that increased life span. To carry out the selective breeding in mice and to fund grants to carry out the genetic analyses of these long-lived mice will require about $1,000,000 per year for a period of up to 10 years. Results from such studies promise to suggest possible interventions to improve the health of older persons.

Frailty--severely impaired strength, mobility, balance, and endurance--significantly diminishes the ability of many older persons to conduct activities of daily living and increases risk of falls and associated trauma such as hip fracture. Thus, long-term care needs could be significantly reduced by preventing or treating these disabilities. NIA, in collaboration with the National Center for Nursing Research, has set aside $2 million per year for clinical trials of interventions to reduce frailty and fall-related injuries. This initiative was the focus of a well-attended October 1989 briefing requested by the House and Senate Aging Committees. A report of this briefing will be published by the GPO. Physical frailty remains a major ongoing NIA research priority. Specific foci include:

Preventing Falls and Fall-Related Injuries. Falls are a major source of morbidity and health costs for older persons, who suffer over 200,000 hip fractures each year, almost all as a result of falls. The resulting costs amount to several billion dollars.

Promoting Functional Independence. Very large numbers of frail older persons need long-term care because their limitations in physical performance (walking, lifting, carrying, climbing steps, etc.) prevent them from shopping, doing housework, using public transportation, and doing other activities of daily living. There is increasing evidence that these limitations are in many cases caused by treatable and/or preventible conditions.

Geriatric Rehabilitation. Many long term care needs of older persons stem from physical disabilities; therefore, an enormous untapped potential for applying rehabilitation techniques in geriatrics now exists. NIA has supported some research in this area, but the number of important unaddressed issues, such as the development of effective approaches for older persons with osteoarthritis and older stroke victims, requires much further development. In May 1989, NIA issued a program announcement encouraging research on biomedical and psychosocial aspects of rehabilitation for older persons. There has been strong interest from the rehabilitation research community in this area.

Osteoporosis. Severely diminished bone strength due to osteoporosis is an important component of frailty. It is because of osteoporosis that falls are so dangerous for older persons: a fall that would produce only minor injury in a person with strong bones will cause a hip fracture in an osteoporotic patient. Research on osteoporosis has reached the point where several nutritional, exercise, and pharmacologic approaches to prevent or reduce this condition could be tested.

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To address the major issue of proper drug prescribing and to diminish problems of adverse drug reactions among older persons, NIA has issued a Request for Applications: "Pharmacology in Geriatric Medicine," for basic and clinical research on the special problems of medication use by older persons. Applications are requested on improved ways to prevent adverse drug effects in older persons, as well as development of better treatments for diseases and disabilities among the geriatric population. Interest in this initiative is extremely high among the research community.

Increased research attention is needed on the problem of cardiovascular disease in older persons. Despite progress in preventing cardiovascular disease in middle age, important questions remain about the effectiveness of current prevention strategies for older persons. Evidence indicates that new strategies, based on increased understanding of the relationship of aging to vascular disease, will be needed for optimal prevention of this major cause of death and disability among older persons. NIA is developing an initiative for support of research in this area beginning in FY 1991.

Feeding mice and rats low calorie diets (without malnutrition) greatly extends longevity, decreases the incidence of late life diseases, and retards rates of change for most age-sensitive biologic measures tested to date. These actions of low calorie diets on aging and disease processes are unmatched by other interventions. Thus, feeding rodents low calorie but nutritious diets provides the best model available to study the biology of decelerated aging. Studies on low calorie diets are a high NIA priority because this model may allow identification of critical aging processes which must be altered to extend health and life and; optimal calorie intakes could forestall aging and diseases in humans. A research initiative for funding in FY 1991 is being prepared to support studies to elucidate mechanisms by which caloric reduction retards aging and diseases.

Approximately 15 to 30 percent of community-dwelling older people and at least one-half of all nursing home residents suffer from incontinence. The monetary costs of managing urinary incontinence are conservatively estimated at $10.3 billion annually, and the psychosocial burden of urinary incontinence is great. Following the recommendations of the recent NIH Consensus Development Conference on Urinary Incontinence, in 1989 NIA issued a Program Announcement: "Research on Urinary Incontinence and Other Urinary Dysfunction in Older Persons" to encourage needed research on all aspects of this problem.

Nutrition is a broad field which cuts across all of the NIA programs and includes laboratory, clinical, behavioral, and social research. Research on nutrition and aging is currently focused in two general areas. One involves determining the nutritional requirements and nutritional status of aging populations, while the other concerns the extent to which diet can influence aging processes and related pathologies. Of particular importance are age-related changes in body composition are characterized by a loss of lean body mass, bone mineral, and total body water with an

accompanying increase in body fat. These changes can alter the need for energy and affect the risk for chronic diseases including heart disease, diabetes and possibly cancer.

Research is being supported on studies that elucidate the biochemical, physiologic, genetic, and molecular events of aging and of age-related diseases. The emphases in these four areas are being coordinated to provide a concerted attack on mammalian mechanisms of aging and results to help identify and validate biomarkers of aging.

Progress has been made in understanding the decline in the immune system with age. It has been found that in older persons a smaller percentage of the lymphocytes are responsive to inducers of cell proliferation than in younger persons. Because lymphocyte proliferation is necessary for an appropriate antibody response, older persons have a decreased ability to form antibodies to combat infections. However, they are not deficient in their ability to recognize a wide variety of antigens. This suggests that if the ability of lymphocytes to proliferate upon stimulation with antigens could be restored in older persons, then the ability of their immune system would also be restored.

Neuroscience and Neuropsychology of Aging

This program fosters and supports extramural and collaborative research and training to further the understanding of the aging process relevant to the neurosciences and associated areas of the psychological sciences. An important component of this program is the support of basic, clinical, and epidemiological studies of Alzheimer's disease (AD) and related dementias of aging. The NIA legislative mandate provides specific authority to the Institute to support research on AD, establish Alzheimer's Disease Research Centers, establish an Alzheimer's Disease Patient Registry, conduct clinical trials for the treatment of AD, and promote research on the diagnosis and epidemiology of AD.

AD is one of the most prevalent, devastating and costly diseases of later life. Research is being supported to determine the cause(s) of AD and of the pathophysiologic chain, which results in the multiple abnormalities seen in AD. Leadership and Excellence in Alzheimer's Disease (LEAD) awards have been made to distinguished senior investigators who have made significant contributions to biomedical research related to AD and other dementias. The Alzheimer's Disease Research Centers have become an exceptional vehicle for the rapid exchange and transfer of scientific information and for facilitating collaboration between centers.

While progress is being made in understanding AD, we do not yet know the cause(s). Research efforts are being concentrated on understanding the role of calcium in AD, the changes in the constituents of cellular membranes in normal aging and AD, and in understanding the mechanisms leading to cell death in AD. In making an accurate diagnosis of AD, research is addressing the incidence, prevalence, and risk factors for AD and other dementing disorders of later life, which will lead to understanding the cause(s) of AD.

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Treatment and management of patients with AD is an important priority for NIA. Pharmacologic, behavioral or environmental interventions are being developed focusing on the patient and his/her behavior. Although at present we may not be able to prevent, treat, or interrupt the course of the disease, we can develop the technologies to preserve function, reduce excess disability and improve symptoms such as wandering, insomnia, pacing, agitation, feeding difficulties, and incontinence, and to reduce the burden to the families of the victims. An NIA-supported project is now studying the safety and efficacy of tetrahydroaminoacridine (THA), an experimental drug which may help control memory loss in some patients with AD. Even modest improvement in functioning by Alzheimer victims would be very rewarding. The continued development of new and novel therapies of an AD remains a high priority for the Institute.

Recent studies on the molecular genetics of AD have shown that there is a linkage between chromosome 21 and the familial or early onset (but not the late-onset) form of AD. This linkage involves a gene locus separate from that of Downs Syndrome (DS) and the beta-amyloid regions of this chromosome and is not associated with a duplication of this region as is found in DS. Further research is needed to pinpoint more precisely the gene loci on this and other chromosomes and, if successful, to identify the proteins coded for. An additional challenge would be to determine the role--particularly, the pathologic effects, if any--of the amyloid protein in this disease.

In children and to some extent in young adults, the brain has the capacity to reorganize itself in response to changes in sensory input or following injury due to trauma or disease. This capacity, called plasticity, appears to be diminished in older individuals although rigorous studies of plasticity in aging have only recently begun. Much more information is needed about changes in plasticity with aging and whether plastic properties of the nervous system can be stimulated by agents such as growth factors which then might be useful in treating brain dysfunction in the aging person.

Progress made in the neurosciences and neuropsychology of aging is helping to unravel the mysteries surrounding the processes of normal aging. One of the most critical issues in the neuroscience of aging concerns the specific mechanisms of selective cell loss in brain and in the ways by which the brain attempts to compensate for these losses. Neuronal death is especially critical due to the inability of most cells in the adult brain to replicate. These losses are hallmarks of many of the age-associated disorders of the brain. It is not known why brain cells die in AD, why specific types of cells in particular brain regions are vulnerable to cell death, or whether or not such cell death can be averted by pharmacological means. The NIA is stimulating and supporting research into several very promising leads concerning the possible mechanisms of neuronal cell death: infectious agents, toxins, abnormal proteins, metabolic abnormalities, changes in cell membranes and membrane receptors.

A major goal of the neuropsychology of aging is to develop a better understanding of how the aging brain, healthy as well as diseased, learns,

remembers, and processes information. Aging has been shown to produce a generalized proportional slowing of all cognitive operations. Recent results suggest that although Alzheimer's disease does act to slow most cognitive operations by a constant proportion, in comparison to the young, some cognitive operations are disproportionately impaired by this disease. This difference in the effects that normal aging and Alzheimer's disease have on the speed of cognitive performance suggests that Alzheimer's is neither a component of normal human aging, nor a simple exaggeration of the processes that occur in normal aging. A more accurate understanding of the specific nature of cognitive deficits may aid medical personnel and family members in their efforts to care for patients with cognitive loss due to this age-related neurological disease.

Research initiatives on cognitive processes and assessments are being aimed at improving and sustaining intellectual function well into the later adult years. Attentional deficits have been found in normal as well as in abnormal aging. A better understanding of the neural basis of attention, as well as the development of ways to treat attentional disorders, could correct some of the short-term memory impairments seen in older adults. Recent neurobiological approaches are providing new ways of exploring the interplay of motivation and cognition in the aging nervous system.

Disorders of sleep afflict over half of the people 65 and older who live at home and about two thirds of those who live in long-term care facilities. Problems in nighttime sleep and daytime wakefulness disrupt not only the older person's lives but also those of their families and caregivers. People over 65 years of age now constitute almost 13 percent of the American population but consume over 30 percent of all prescription drugs dispensed, as well as an unknown percentage of over-the-counter medicines. A large proportion of these drugs are sleep medicines and hypnotic agents, the safety and efficacy of which have not been established for older people. Nor has it been established to what extent drugs contribute to or alleviate their problems of sleep. It is necessary to understand the causes of these disorders and to develop better treatment strategies, including non-pharmacological methods, to correct them.

Hearing losses in the form of presbycusis and loss of speech intelligibility form a major cause of loss of quality of life in the elderly. It has been estimated that 30 percent of adults aged 65 through 74 and more that 50 percent of those over 75 have some degree of hearing loss. Thus, hearing losses associated with the process of aging (termed presbycusis) affect about 9.2 million people in this country. The elucidation of the underlying physiological and cognitive mechanisms mediating those changes needs expanded research efforts in order to learn how the auditory system ages, what is to be expected as normal hearing and speech perception, and wherever interventions can be applied to correct age-related deficits.

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Behavioral and Social Research

This program supports research and training through all award mechanisms on social and behavioral factors that affect both the process of growing old and the place of older people in society. It focuses on how people grow older, on the interrelationships between older people and social institutions (e.g., families, health care systems), and on the impact on society of the changing age-composition of the population.

It is well-established that the family is the primary contributor to health, functioning, and psychological well-being of both children and older people. Yet, dramatic changes in the family portend further changes in the extent and form of support across generations, as exemplified in: increasing longevity of family members; low rates of fertility; high rates of divorce, remarriage, and single parenthood; high rates of female labor force participation; and loss of the traditional roles for men and women. These changes challenge existing bases of both emotional and instrumental support for aging relatives. Interdisciplinary research continues, therefore, to explore changes in patterns of family interaction; living arrangements; help and services (e.g., family caregiving and financial aid); family solidarity and strain; cohort differences as particular events in one generation affect family members in other generations; and broad fiscal issues of intergenerational equity. This research is needed as a guide to professional practice and public policy related to older people.

Recent governmental and non-governmental reports highlight the special health-care and other service needs of rural people and especially the needs of those who are old. People in rural areas are more likely than their urban counterparts to be in fair or poor health, to suffer from chronic or serious illness, and to be without a regular source of health care and health insurance. Moreover, a higher proportion of deaths occur among the nonmetropolitan than the metropolitan population over 65 years of age. The NIA plans to establish two centers on rural health and aging to examine the particular problems of older adults living in rural areas.

At the same time that our nation confronts a critical shortage of available workers, increasing numbers of able older persons are spending two to three decades of their lives in retirement. Many older people, however, want and are capable to continuing some form of productive activity. They comprise an untapped national resource. Research is needed to examine how current unprecedented trends in work, retirement, and productivity affect the physical and psychosocial functioning of aging individuals, and also result in losses of productivity for society and older people themselves. Studies are focusing on: redesigning paid and volunteer jobs; productivity in family roles; retraining; spreading education, work, and leisure more evenly over the life course; social, economic, and personal factors influencing early retirement; and innovative approaches for matching the growing numbers of older people with rewarding opportunities for productive activity.

As part of its initiative on health behaviors and aging, the NIA plans to strengthen current attention to the social and psychological

aspects of several specific health behaviors such as nutrition, drug-taking and oral health. Several studies are examining the biosocial linkages between health and behavior in old age (e.g., how social or psychological factors operate on intervening immunological processes to affect susceptibility to disease).

Current plans for a national survey on self-care behaviors will analyze the extent of self-care practices, factors predicting self-care behaviors, health consequences of different behaviors, and the link between self care and formal health care. Also important is an understanding of older people's perceptions about aging and their reactions to health and illness. NIA funded research has shown how attributions of symptoms (e.g., aches and pains) to aging rather than illness can delay potentially remediable care. More research is needed on how older people and their care givers define health and functioning--and how social factors are individual personality characteristics determine health seeking actions.

The Federal Forum on Aging-Related Statistics continues to increase collaboration and communication, especially in the areas of linkage to administrative records, sharing and planning of surveys, standardization of measures, consideration of the NAS Report on Statistical Data for an Aging Society, etc.

Data resources will continue to be developed and special attention will be focused on the development of linkages to administrative data files, to issues of developing access to restricted data without breaching confidentiality requirements, to improving the quality of data on the 85 plus population, and ensuring that sample sizes are adequate for analysis of this population. The NIA is developing a multi-agency consortium for the support of a new longitudinal survey of health and retirement. This survey will provide current and reliable data on the retirement process and its consequences. NIA is also planning to improve a number of major longitudinal surveys (such as the Panel Study on Income Dynamics, the National Longitudinal Surveys older Cohorts, and the Consumer Finance Survey) for aging research by adding modules to ensure that these surveys will include adequate data on health and economic factors by adequate samples of the elderly (especially the oldest old).

Recent projections made by some of these studies suggest that the Census Bureau's forecasts may severely underestimate the future members of the oldest old, perhaps by as much as 50-100 percent. Once the 1990 census is completed, a more solid basis for additional projections will become available. A major effort is being mounted to develop measures of active life expectancy.

Loss of the ability to function effectively in everyday life is probably the central factor precipitating the need for caretaking and other services by the older population. Understanding the trajectories in decrements and improvements in the ability of especially the Oldest Old to function in everyday life, and identifying the appropriate risk factors, are essential first steps in the development of appropriate prevention and intervention programs designed to increase the ratio of

active to disabled life expectancy. Surveys such as the Longitudinal Study on Aging and the National Long Term Care Survey suggest that over a two-year period, even among persons over age 85, there is considerable regaining of functioning.

Epidemiology, Demography, and Biometry

This program collects and analyzes epidemiologic, and demographic data relevant to specific diseases and conditions affecting older persons. National and international epidemiologic longitudinal and comparative studies and research on special populations are of special interest. Data collected as a result of these efforts are being analyzed for their implications for enhancing our knowledge regarding aging processes as well as opportunities for interventions to reduce frailty and increase independence of older populations.

Important findings were reported using data from the NIA's multi-center prospective study, the Established Populations for Epidemiologic Studies of the Elderly (EPESE). A prospective study examined the extent to which a wide array of characteristics predict utilization of an important long-term care (LTC) service and medical home care. The overall age-sex adjusted rate of 2-year incident home care was 3.2 percent. For both men and women, the rates among the aged 85 or older group were approximately 12 times the rates of these aged 65-74. Predictors of incident home care included: receiving help with at least one activity of daily living, being dependent in certain defined functional health areas, being homebound, more errors in mental status items, and no involvement with social groups.

Three measurements of peak expiratory flow rate were obtained, indicating that peak expiratory flow rate was strongly related to age, sex, smoking, and years smoked. After adjustment for these factors, low peak expiratory flow rate was associated with chronic respiratory and cardiovascular symptoms; and with certain cardiovascular variables. No significant associations were found with history of myocardial infarction or systolic and diastolic blood pressures. Peak expiratory flow rate was positively related to education and income and also was strongly related to measures of functional ability and physical activity, self-assessment of health, and simple measures of cognitive function. The correlations of peak expiratory flow rate with pulmonary symptoms and other indices of chronic disease raise the possibility that peak expiratory flow rate will predict mortality in an elderly population.

Prevalence of the use of medications that may affect dental health and dental treatment was reported. Nine categories of possible drug effects were created. Seventy-seven percent of the population reported taking at least one medication with potential importance for the dentist. Fifty-one percent reported being on medications known to cause oral discomfort associated with reduced salivation, 39 percent reported medications possibly affecting blood clotting, 28 percent were at risk of drug-induced soft tissue reactions, 22 percent reported medications which could interact with drugs used commonly in dentistry, 20 percent reported medications requiring that vasoconstrictor use be minimized, and 16

percent reported medications indicating reduced stress tolerance. Dentists must be knowledgeable about their patients' medications and their important side effects. This is especially important among the elderly who use more drugs per capita than do other age groups.

The social and psychological consequences of living with a cognitively impaired spouse were assessed among community-dwelling elderly individuals. Principal findings were that cognitive impairment in wives is significantly associated with husbands who show symptoms of depression whereas cognitive impairment in husbands is only weakly associated with wives who show symptoms of depression; decreased participation in social/leisure activities is selectively related to spouses level of cognitive functioning among both men and women; while shared by both men and women, this research has demonstrated that the relationship between wives cognitive impairment and husbands' depressive symptoms is influenced by perceived availability of financial support from friends and relatives, but not by activities of daily living limitations in wives, lack of emotional or instrumental support from wives, household responsibilities among husbands, or lack of participation in social/leisure activities in husbands.

The prevalence of angina pectoris (chest pain) and its association with coronary heart disease risk factors and manifestations were investigated in representative samples of the U.S. population. The study populations included black and white subjects aged 25-74 years examined in the NHANES II, 1976-1980 and Mexican-American subjects aged 25-74 years examined in the Hispanic HANES, 1982-1983. Age-adjusted prevalence rates of angina were similar among black, white and Mexican-American women. Compared to men, an excess prevalence of angina among women was observed among white and Mexican-American persons under age 55, but not over age 55. Because many younger women with chest pain who may consult with physicians are likely to have elevations in cardiovascular risk factors, their self-reported chest pain can be used as an opportunity to intervene and reduce future risk of cardiovascular disease.

Long-Term Care

The NIA has had a longstanding interest in social and behavioral aspects of long-term care, and supports a growing Institute-wide research program on issues related to the need for and use of medical and non-medical long-term care. The NIA long-term care research agenda now includes a major emphasis on health outcomes or effectiveness research. General areas of research include: predictors of the need for, and use of, long-term care; the organization and use of innovative forms of community and institutional long-term care; the effectiveness of different packages of health care and supportive services for reducing or eliminating the need for long-term care; and the dynamic nature of long-term care (e.g., the linkage between informal care and formal care; the movement through the health care system over the course of illness. Special attention is being paid to the development and community services, including respite care, board and care, and in-home health care.

Biomedical and behavioral research on long-term care remains a major NIA priority. NIA's Teaching Nursing Homes support extensive research on

clinical problems of older persons in long-term care settings, and have made important findings on dementia, nutrition, falls, urinary incontinence and other disorders. In addition, NIA's new initiatives on physical frailty and injuries, geriatric rehabilitation, geriatric pharmacology, and urinary incontinence offer the promise of new ways to significantly reduce long-term care needs.

Training

The growing population of older persons will require an expanding body of biomedical, social, and behavioral scientists conducting basic research on aging processes and the social conditions of older people in order to provide a sound scientific foundation for geriatric practice and social policies in the future. Moreover, many more geriatricians and other health care providers with geriatric training will be needed. The current shortage of well-qualified academic leaders in geriatrics limits the capacity to train these personnel. Because of this, the Institute of Medicine in 1987 recommended centers of excellence to train academic leaders in geriatrics. Accordingly, NIA created the Claude D. Pepper Geriatric Research and Training Centers (GRTC) program, and in FY 1989 made the first award to the University of Michigan. NIA plans to make an additional award in FY 1990. At least 10 academic centers have the capacity to organize high quality GRTCs.

The NIA is also initiating two other new awards--the Geriatric Research Institutional Training Award and the Geriatric Academic Program Award--for the development of geriatricians with the research abilities needed for academic leadership. These two awards provide geriatricians with a continuum of career development support to achieve independent academic status. They thus complement the core resources offered by the Claude D. Pepper Geriatric Research and Training Center award.

To promote research career development in the especially important field of rehabilitation and aging and alleviate the severe shortage of researchers in this area, NIA will introduce an ongoing program supporting Special Emphasis Research Career Awards in Aging and Rehabilitation. These will provide five years of support to acquire combined research expertise in these fields.

National Institute on Aging

Intramural Research

Authorization: Indefinite

Budget Authority:

1990 Appropriation		1991 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA
243	$28,292,000	250	$30,558,000	+7	+$2,266,000

Purpose and Method of Operation

The Intramural Research Program conducts basic and clinical research within the NIA. The majority of the research is conducted at the Gerontology Research Center in Baltimore; the Laboratory of Neurosciences is located in the Clinical Center on the NIH campus. This activity also supports the operations of the Epidemiology, Demography and Biometry Program.

Rationale for Budget Request

The 1991 budget request for Intramural Research is $30,558,000, an increase of $2,266,000 over the FY 1990 estimate of $28,292,000.

The Baltimore Longitudinal Study of Aging (BLSA) is the NIA's major intramural study of human aging, now in its 32nd year. Approximately 1100 men and women ranging in age from 19-97 return every other year to be assessed in over 50 continuing studies of age changes in physiological and psychological functioning. In addition to studying the active participants, over 400 formerly active participants were contacted to determine health and cognitive status and efforts are made routinely to obtain accurate information on cause of death for deceased participants. The overall goal of the BLSA is to provide a scientific description of aging, to distinguish these changes from factors associated with disease and environmental changes, and to relate the observed changes to underlying biological mechanism.

Studies of health/disease relationships seek to describe the natural history of disease processes. During FY 1989, studies of the development of benign prostatic hypertrophy, and the relationship between expected and unusually accelerated age declines in pulmonary function in relation to ischemic heart disease were completed. The BLSA may help us understand the natural history of health promotion policy because participants are in general well educated and have adopted more healthy lifestyles by lowering blood pressure and cholesterol and by changing diet and exercise over the history of the study. Age specific differences in the importance and meaning of some risk factors at given ages have been found.

Located in the NIH Clinical Center, the Laboratory of Neurosciences focuses on basic and clinical studies on brain function as altered by age and diseases such as Alzheimer's disease and Down's syndrome. They have characterized the changes in central nervous system activity using state of the art technology including PET and serial quantitative CAT scans. These studies have established that the dementia occurring in some 30 percent of Down's syndrome individuals after the age of 40 is identical to that observed in the familial and common forms of Alzheimer's disease. Unique and reliable methods using PET, psychological and CAT scanning have been developed for diagnosing and following the course of Alzheimer's disease. These methods are being used to conduct clinical trials on drugs to replace the stimuli of cholinergic centers affected in this disease. Also, since there exists a barrier to the free penetration of pharmacological agents into the brain, "the blood brain barrier," scientists in the Laboratory of Neurosciences have developed novel modifications for drugs that allow their penetration to the site needed. These studies are supported by basic research on the brain.

The Laboratory of Biological Chemistry is currently developing new programs including studies on gene regulation in cartilage and blood vessel cells in response to age and disease. Additionally, attempts will be made to develop a neurobiology group to define age-associated changes in brain function predisposing to Alzheimer's disease and other forms of dementia. The growth and spread of cancer cells is being studied in aged animals, since most cancers occur in old individuals. Some studies will continue on the homeostatic mechanisms controlling mineral metabolism as it relates to osteoporosis.

The Laboratory of Cardiovascular Science studies factors that may underlie changes in the heart and the vasculature in aging and in disease. Cardiac hypertrophy, commonly observed in aging individuals, has been shown to be due to hypertension and not to the aging process. However, clear alterations in ion flow, particularly calcium ion, have been observed in the aging heart which relate to changes in function. These changes offer a clear approach to studying the molecular basis of aging of the heart and a system in which to measure the heart's response to various therapeutic modalities. Recent studies have shown the high value of stress tolerance tests, using electrocardiograms and thallium scanning in predicting the likelihood of a coronary event in the next 4-5 years--essentially the same high confidence in <u>not</u> having a coronary event in men aged 60-69 as in those age 40-59, if the stress test is normal.

Research in the Laboratory of Clinical Physiology focuses on the complex interactions of physiological aging processes with lifestyle variables (diet, body composition, physical activity) and with specific disease states. With advancing age, the immune system undergoes a general decline. Accompanying this deterioration are a wide variety of clinical diseases clearly caused by immune system dysfunction. Since the causes of the age-associated decline in immune function are poorly characterized, their cellular and molecular origins are being actively investigated to identify areas amenable to enhancement or correction. Ultimately, this work may lead to programs for the modification, therapy

and possible prevention of age-associated diseases through the development of vaccines and/or vaccine protocols specifically designed to overcome the ineffectiveness of the immune system of the elderly.

Very basic changes are known to occur with aging at the cellular, genetic, and molecular level. Integration of these changes is importantly controlled by the endocrine system. A comprehensive analysis of neural-endocrine system is in progress to define the locus of many changes that occur with aging in the hypothalamus, the pituitary gland, and other endocrine target organs. In addition to observational studies in the free-living BLSA population, more intervention research is now being conducted. The differential effects of sex hormones administered by mouth and by skin patches to post-menopausal women will provide data on the relative risks and benefits of this new technique of hormonal therapy.

Scientists in the Laboratory of Cellular and Molecular Biology conduct research on the biology of the aging process as well as on fundamental molecular biological systems that are basic to understanding this process. One project seeks to clarify the mechanism of bond formation in RNA synthesis, one of the three steps in genetic information transfer. Another project has focused on some of the precise mechanisms by which signal transduction and gene expression elicited by various stimuli are altered during aging to result in physiological and behavioral changes. In these studies, various interventions (e.g., drugs, transplants and dietary manipulation) are employed in attempts to prevent, halt, or reverse such age-related dysfunctions. Research using magnetic resonance techniques is being conducted on the effect of age on metabolic changes that occur during exercise.

The Laboratory of Molecular Genetics utilizes recombinant DNA technology to study the regulation of cellular activity as related to aging. Recently, scientists have isolated and characterized a new gene that stops cells from proliferating. A role for this gene in the control of cell division and in cellular senescence is postulated. The ability of cells to respond to heat stress and DNA damage is also being evaluated. These studies suggest a diminished capacity of aged cells to respond to such factors consistent with a generalized reduction in the capacity for adaptive responses in the aging organism.

Studies in the Laboratory of Behavioral Sciences have shown unequivocally that it is possible to train hypertensive patients to lower their blood pressure and to maintain these reductions for at least one year. Furthermore, it has been shown that the medication needs of many of these patients can be reduced. A pilot study has shown that the Behavioral Stepped-Care treatment procedure can be applied effectively to patients with isolated systolic hypertension. In addition, other studies in this Laboratory have shown that it is possible to effectively treat urinary incontinence in community-dwelling elderly persons by training them to control their bladders and/or sphincters. A number of American and European health care professionals have trained at this Laboratory, and they are successfully treating patients in their own facilities.

Building upon evidence that personality has a crucial influence on health and aging, the Laboratory of Personality and Cognition asserts

that personality should be assessed as a standard part of health workups. Recent findings suggest that antagonistic hostility (seen in cynicism and rudeness) is a risk factor for coronary disease. By contrast, neurotic hostility (seen in resentment and irritability) is not. This finding illustrates the value of basic research on personality in making crucial distinctions, and it has important implications for predicting coronary outcomes.

The Epidemiology, Demography and Biometry Program staff have published a number of scientific studies using data from the National Health and Nutrition Examination Studies (NHANES) and the NHANES I Epidemiologic Follow-up Study (NHEFS).

Data from persons age 45 or older in the NHANES, 1971-74, showed that subjects with lens opacifying disease had an increase in odds for age-related macular degeneration (AMD) compared to those who had no lens opacities. These data are consistent with the hypothesis that light-induced damage may contribute to both lens and retinal disease and suggest that cataract extraction without implantation of ultra-violet blue light absorbing intraocular lens may place subjects at increased risk of AMD.

The occurrence of pressure sores (decubitus ulcers) during a follow-up period of approximately 10 years is documented for the NHEFS Cohort aged 55 to 75 years at baseline. During the follow-up period, pressure sores were identified in 1.7 percent for those aged 55 to 69 at baseline and rose to 3.3 percent for those 70 to 75 years old. Risk factors for pressure sore development were evaluated using data collected in NHANES I at baseline. Significantly increased risk for pressure sore development was found for those who at baseline were current smokers, reported being relatively inactive, had poor self-assessed health status and who were found on physician's exam to have dry or scaling skin.

Projections of future populations are fraught with uncertainties based on past fertility and immigration trends, assumptions about medical science and lifestyles. The U.S. Census Bureau and the Social Security Administration may be unduly cautious in their assumption that the mortality decline of the past two decades cannot continue; it may be sustained for the next half century. Findings obtained by EDB investigators using alternative assumptions about rates of mortality and morbidity indicate that the needs for health services, institutionalization, and home care of the disabled elderly, especially among the oldest old, may make ever greater relative and absolute demands on the nation's health care resources.

Analysis of National Health Interview Survey, Supplement on Aging (SOA) data on comorbidity in the older U.S. population revealed that the percent of the population 60 years and older with two or more of the nine common chronic conditions obtained in the SOA was higher for women than men at each older age. Persons having difficulty or needing help with activities of daily living increased with increasing levels of chronic conditions. Likewise, a linear increase was observed in the proportion of persons experiencing none of the nine conditions as compared to those with five or more of them.

A micro-simulation model was developed to explain and estimate the optimum Medigap insurance coverage for elderly with different levels of insurance premium subsidy. The Medigap risk exposure was estimated from the 1977 National Medical Care Expenditure Utilization Survey.

National Institute on Aging

Research Management and Support

Authorization: Indefinite

Budget Authority:

1990 Appropriation		1991 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA
126	$13,751,000	131	$14,760,000	+5	+$1,009,000

Purpose and Method of Operation

This activity provides administrative support and program guidance for the grants and contracts awarded under the aging activity. Facility support costs and related general expense items essential to all of the Institute's Research programs are funded by this activity. In addition, salaries and other related expenses are paid from this account.

Rationale For Budget Request

The FY 1991 budget request for Research Management and Support is $14,760,000, an increase of $1,009,000 over the 1990 current estimate.

This budget activity will continue in FY 1991 to provide leadership and guidance for the Institute grant program. Support for the National Advisory Council on Aging, which provides policy recommendations and scientific expertise on grant applications continues to be a major priority under this activity. Efforts by the NIA will also continue toward the development of more effective ways to address the programmatic and administrative needs of aging research.

In carrying out its Congressional mandate to coordinate aging research, the NIA serves as permanent chair of the ad hoc Interagency Committee on Research on Aging and remains a major source of information exchange for activities related to research on aging throughout the Department and the Committee's other member agencies. During the last year the Committee has focused on the following topics of home health care for older people, update on activities related to Alzheimer's disease, and gaps in data sources for studies of aging, and rehabilitation and aging. The ad hoc Interagency Committee, the Federal Forum on Aging-Related Statistics, and the Gerontological Society of America jointly prepared and distributed a compendium of inventories of aging data.

The NIA increased its efforts in the past year to expand the number and quality of projects focused on minority aging. The NIA Work Group on Minority Aging was established to help identify research priority areas,

increase short and long term training of minority investigators, and serves as a major link to the minority community for the dissemination of aging-related information.

In its recognition of the importance of international cross-cultural studies of aging, the NIA has submitted plans to establish an Institute-wide staff committee for international research on aging. The committee will be asked to provide a coordinated approach to bilateral and multilateral activities such as the October 1989 initiative on "Health of Older Persons" recently submitted through the NIH Fogarty International Center for consideration by the Department in connection with the Public Health Service Strategic Plan for International Health. Other areas that are expected to be advanced for international collaboration include studies in the Pacific Basin, Latin America, and India; response to congressional report directives with the U.S. Agency for International Development (AID); expansion of the U.S. Bureau of Census International Data Base on Aging; and exploration relating to the U.S. State Department and U.S.S.R. initiative on health of the elderly.

The NIA sponsored the Summer Institute in Research on Aging for the third successive year. The objective of the Summer Institute is to recruit new investigators to careers in research on aging through the provision of an overview of current knowledge regarding aging and the identification of issues and opportunities for further research in this area. Several of the past participants have applied to NIA for support of their research on aging, and/or have accepted employment with the opportunity to pursue aging related research. The NIA plans to continue sponsorship of this training activity.

As directed by the Omnibus Health Bill, P.L. 99-660, NIA will be awarding a contract to establish a national "Alzheimer's Disease Education and Referral" (ADEAR) Center to gather, maintain, and disseminate information on Alzheimer's disease research and services. Upon award of the contract, the ADEAR Center will distribute information about Alzheimer's disease to health professionals, patients and their families, and the general public. Center staff will respond to written and telephone inquiries from a variety of audiences and provide information about the diagnosis and treatment of Alzheimer's disease, research, and organizations that provide services to patients and their families. A computerized data base will enable staff to access the most up to date information on the disease; in addition, the Center will revise existing and develop new publications about Alzheimer's disease. The Center will carry out health education activities for health care professionals and the public, including the development of print and audiovisual materials and the development of strategies for the implementation of full-scale national health education campaigns.

National Institute on Aging

Detail of Permanent Positions

	1989 Actual	1990 Appropriation	1991 Estimate
ES-4	5	7	7
ES-3	1	1	1
ES-2	1	1	1
Subtotal	7	9	9
GS/GM-15	18	18	18
GS/GM-14	16	16	16
GS/GM-13	26	29	29
GS-12	22	25	26
GS-11	24	28	30
GS-10	0	0	0
GS-9	24	26	28
GS-8	3	3	3
GS-7	23	25	26
GS-6	24	26	27
GS-5	18	19	19
GS-4	7	8	8
GS-2	1	1	1
Subtotal	206	224	231
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant surgeon general grade	1	1	1
Director grade	9	9	9
Senior grade	6	6	6
Full grade	2	2	2
Subtotal	18	18	18
Ungraded	41	41	41
Total permanent positions	272	292	299

National Institute on Aging

New Positions Requested

		1991	
NIA Intramural Research	Grade	Number	Annual Salary
Research Psychologist	GS-12	1	$ 35,825
Chemist	GS-11	1	29,892
Biologist	GS-09	1	24,705
Biologist	GS-09	1	24,705
		4	115,127
NIA Research Management and Support			
Program Analyst	GS-11	1	29,892
Fiscal Analyst	GS-07	1	20,195
Grants Technical Assistant	GS-06	1	18,174
		3	68,261

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Advisory and Assistance Services

For FY 1991, the Advisory and Assistance Services budget will be $1,568,000, an increase of $105,000 over FY 1990. These funds will continue to support a variety of services that will allow the NIA to carry out its mandated mission.

The National Advisory Council on Aging and the Board of Scientific Counselors are mandated activities that the NIA conducts to provide a secondary review of its research programs and proposals. The Alzheimer's Disease Education and Referral (ADEAR) Center will provide information and dissemination of services in support of the NIA's mission to operate a legislatively-mandated Alzheimer's disease education center. The Omnibus Reconciliation Act of 1986 (P.L. 99-660, Title IX) directed the Director of the NIA to establish a clearinghouse on Alzheimer's disease. The primary goal of the Center will be to serve as a national informational resource that provides accurate, timely information on Alzheimer's disease, its consequences and potential treatments, new research and available services to patients and their families, physicians and other health professionals, and the general public. Other goals include: 1) developing a national computerized database of information on Alzheimer's disease, and 2) preparing materials to communicate the nature of the disease, its symptoms, and appropriate methods to care for and assist patients, health care professionals and special target audiences such as public service employees. A second subsection of the law called for NIA to establish a computerized information system concerning State and local government and private programs and services, to translate scientific and technical findings into lay language and make such information available to the public, and to establish a toll-free hotline to make information available upon request. The Summer Institute in Research on Aging for new investigators has been sponsored by the NIA and the Brookdale Foundation for the last three years. Other advisory and assistance services will be needed to evaluate the effectiveness of the Summer Institutes in involving the participants in research on aging. We would review the research and related activities in which the participants are now involved and compare them with activities involved in by those who applied to the Summer Institute but were not selected to participate.

Requests for consultant services in the Institute are forwarded to the Director, NIA during the annual planning and budget request process and are reviewed. A determination is made by the Director, NIA as to the appropriateness of the request, and at that time it is determined if other institute staff can perform the service. Requests are approved through the budget process.

THURSDAY, MARCH 15, 1990.

NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES

WITNESSES

DR. LAWRENCE E. SHULMAN, DIRECTOR, NIAMS
DR. WILLIAM F. RAUB, ACTING DIRECTOR, NIH
DR. ROBERT L. BRUUN, EXECUTIVE OFFICER, NIAMS
MARGARET S. KERZA-KWIATECKI, BUDGET OFFICER, NIAMS
DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DHHS

Mr. NATCHER. Now we take up next the National Institute of Arthritis and Musculoskeletal and Skin Diseases. Dr. Shulman, before we start, tell us who you have with you at the table.

Dr. SHULMAN. Mr. Chairman, thank you very much.

On my left is Dr. Robert Bruun, the Executive Officer of our Institute; and Ms. Kerza-Kwiatecki, our Financial Management Officer.

Mr. NATCHER. We are glad to have all of you before the committee.

We will be pleased to hear from you, Dr. Shulman.

Dr. SHULMAN. Thank you very much, Mr. Chairman. It is a great privilege once again to appear before you on behalf of the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

We have had a good, active year, Mr. Chairman. We have much to do. We have much going on, as described in my written statement to you. As you know, we have a broad, diverse research agenda, addressing so many diseases, all important. These are long-lasting diseases, causing much disability, and they impair the quality of life, as you heard earlier, for many of our people. There is evergrowing interest in these diseases on the part of both the press and the public, and on the part of our medical and scientific communities.

Let me highlight a selected few of these for you, emphasizing progress, achievements, and challenges, Mr. Chairman, as you requested us to do last year. Let us start here. I would like to say from the beginning, Mr. Chairman, that neither I nor Dr. Williams has an interest in Newsweek Magazine, but at the same time, we would like to indicate to you their cover of Lyme disease. This was featured by Newsweek in an issue last May. It stressed that the disease is spread by a tiny tick and stressed on how to protect yourself in the summer by measures we discussed last year. You will remember the photographs we presented then.

Let us turn to the diagnosis of Lyme disease, which still remains a problem. There are many different blood tests that are available all over the country for diagnosis. They are being used everywhere. We still have some problems with them. They are insensitive

and under-diagnose Lyme disease early in the disease. Later in the disease, they over-diagnose the disease. Actually there was a recent article published in the American Medical Association Journal which compared four different laboratories and found poor agreement among them. We have to do better.

We have happily some very new and promising tests as I have listed here. Our grantees have developed a new antibody test in the urine. The Allergy Institute, with their intramural scientists using the polymerase chain reaction, have been able to detect a small number of bacteria. Lastly, we have been able to grow the bug from the blood and even from the heart. We take a piece of tissue from the heart, and we are able to grow the bug from there. These are some of the advances being made in the diagnosis of Lyme disease.

Let's turn to osteoporosis, for which we are the lead institute in the NIH. Nothing is higher on our agenda than research on osteoporosis. It is now clear that exercise is very important early in life for your bones. We have a recent study that shows that physically active 25 to 34 year old women have much higher bone density, stronger bones, than do inactive women of the same age.

We have not such good news in terms of fluoride treatment. That was the great white hope in that fluoride had the clear ability to form new bone, and therefore, the potential to restore lost bone. We started a large clinical trial in '81, with two centers studying the effects of fluoride via a long term trial. This was performed in middle-aged women with osteoporosis. The results of those trials were completed last summer. They show that, yes, fluoride can increase the bone density in the spine by as much as 30 to 40 percent, however, fluorides did not reduce the numbers of fractures of the spine that occurred in these women. That showed very significantly that it is not just the density of the bones of the spine, but rather the strength of the bone, that is important.

On the other hand, we have encouraging results in osteoporosis with other agents, such as calcitonin, cyclophososphamides.

We have joined with the Aging Institute on a study of thiazide drugs; it was found that older people who are taking thiazide drugs for high blood pressure have higher bone densities than those who do not.

We have great hopes from research on growth factors on bone. We have discovered many such growth factors and hope to have this area developed so that new agents can be developed that can create new bone.

The next poster shows some of the do's and don'ts for osteoporosis. You should not be inactive, you should not be a couch potato. Drinking alcohol and smoking cigarettes are bad for your bones. On the other hand, if you get enough good calcium through skim milk, and other sources, and you dance up a storm, you can dance to the stars.

Newsweek also had a fine, comprehensive article on arthritis last year. There is a bit of error on the cover. Thirty seven million Americans suffer from not one disease but over 100 different types of arthritis. By the way, the cover shows a young woman with rheumatoid arthritis, a major crippling disease.

It says there is no cure but new treatments offer hope. This is so true. I want to share with you some of the treatments available for the treatment of rheumatoid arthritis.

We can do a great deal for patients right now. Coated aspirin and nonsteroidal anti-inflammatory drugs, ibuprofen, and the like, are helpful.

If they don't work, we have secondary drugs. Gold compounds, antimalarials, and penicillamine. They have all been shown to be effective. Cortisones, such as prednisones, are back in vogue. I have had good success treating patients with low doses of prednisone and aspirin.

For those who have not responded, immuno-suppressive drugs may be used. The first two, azathioprine and cyclophosphomide are powerful, effective, but may be toxic. Methotrexate has been shown to be effective and largely safe. It has been approved by FDA for the treatment of rheumatoid arthritis. We have more agents down the pike as well.

In terms of lupus, which you can see in this picture, is a serious disease of young women. It is an inflammatory immune-mediated disease. Thirty years ago the outlook for this young lady would be that she had a 50 percent chance of dying five years after diagnosis. Today, she has an over 90 percent chance of surviving ten or fifteen years after diagnosis.

We have made great strides in this disease, sir, as a result of a whole host of discoveries. We have had some additional major advances this year, uncovering specific disturbances of the immune system, auto-antibodies. We know why lupus women have more miscarriages, and we can do something about it.

But we still have some major questions with respect to lupus: why women nine to one; why black women three to one; and why does this affect young women primarily?

Does lupus run in families?

What is the key role of the antibodies and what are the agents or injuries that start it off?

We are planning a major conference to address these residual and major questions with respect to this very serious disease of young women.

My last cover is from Science News. This article is entitled "Wrestling With Wrinkles." I will ask you and your colleagues on the dais to guess which of these two people are older.

Mr. NATCHER. The one on the left.

Dr. SHULMAN. You are a very clever gentleman. You go to the head of the class.

Mr. NATCHER. Thank you.

Dr. SHULMAN. The woman on the right is a 62 year old Native American woman, who spent most of her life outdoors. The person on the left is a 91 year old Zen monk from Japan, who has rarely seen the light of day. So the moral here, sir, is that it is good to stay in the dark and remain unenlightened.

I want to report to you on a highly successful consensus development conference we held at NIH last year on sunlight and the skin. It was a very highly held conference, arousing a great deal of interest. I am sorry to indicate to some of you here that the sun overall really damages the skin, except for what it does to produce

vitamin D. And for that only the tip of the smallest finger has to be exposed for an hour each day.

The panelists reported that say once you get a tan, you have already damaged your skin.

Dr. SHULMAN. This poster points out some things that make you susceptible to sun damage. There are obviously ethnic factors and genetics; and diseases like lupus. All of this can be prevented by sunscreens, and we learn that that number on the sun screen, the sun protective factor, the best number is 15: numbers 2, 3, and 4, that is not enough protection. They now have them up to number 49, but you don't need to go that high. Fifteen seems to be just right.

Protective clothing is excellent. You ought to wear a broad brimmed hat, such as a panama hat. In taking a word from Noel Coward, one should stay "out of the midday sun".

We learned at the conference that 50 percent of the sun exposure that an average person in this country has, has been attained by the time they are 18 years old. We can prevent some of that sun damage by having the outdoor activities at school take place after 3 o'clock in the afternoon. Between 10 a.m. and 3 p.m., one gets 60 percent of the day's sun exposure.

The damage is treatable. This was a very highly successful conference. Our chairman had a very interesting program on television. It was an important event.

As you know, Mr. Chairman, we have resource advances in several other areas. They are osteoarthritis, sjogren's syndrome, scleroderma, arthritis of the spine, back pain, Paget's disease of bone, sports medicine, muscle biology; epidermolysis bullosa, osteogenesis imperfecta, and other heritable connective tissue diseases; psoriasis, vitiligo, alopecia, and AIDS.

We have a large agenda. We have some encouraging new developments in our intramural research program that are also very important to us.

Mr. Chairman, the budget request for our institute is $176,080,000. I will be glad to answer any questions that you have.

[The statement of Dr. Shulman follows:]

Statement of the Director
National Institute of Arthritis and Musculoskeletal and Skin Diseases

It is my great privilege to share with you some of the accomplishments, latest research advances, and opportunities for research by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) this past year, and to present some of our plans for the future. The mission of the Institute embraces a wide variety of disorders; most of which are long-term and disabling. These diseases affect millions of Americans, exacting an enormous toll in human suffering and placing an immense economic and social burden on the Nation.

One of the most rapidly growing problems is Lyme disease, which affects many parts of the body and is caused by screw-shaped bacteria that are transmitted by ticks. Some 5,000 new cases were reported last year; and it is increasing. Because its symptoms closely resemble those of other illnesses, early diagnosis of Lyme disease is often difficult. We are hopeful that a urine test, developed by our researchers, that uses highly specific antibodies will prove to be a better diagnostic instrument than the blood tests now available. Another promising lead has emerged from a US-USSR study, showing the existence of Lyme disease in different regions of the Soviet Union, and apparent differences in the strains of the causative bacterium in the different regions. This could explain regional differences in the expression of Lyme disease.

To encourage more research on Lyme disease, the Institute has issued, jointly with the National Institute of Allergy and Infectious Diseases, a request for applications pertaining to its pathogenesis. The NIAMS has also issued a program announcement focusing on clinical and epidemiological research on Lyme disease. The responses to these two initiatives have been highly encouraging.

Rheumatoid arthritis is of major concern to our Institute and to the 2.1 million adults in the United States who suffer from it. Good news with regard to the treatment of this potentially crippling disease was establishing the efficacy of methotrexate. Definitive therapeutic trials have reconfirmed its safety, and the Food and Drug Administration has recently approved its use for treating arthritis.

This year, the NIAMS is initiating a multicentered clinical trial of minocycline (a form of tetracycline) for the treatment of rheumatoid arthritis. It is based on the recent demonstration that minocycline inhibits the activity of collagenase--an enzyme that breaks down cartilage and bone in the joint. If the drug proves beneficial, investigators might then develop and evaluate a new form of tetracycline that retains the collagenase-inhibiting properties of minocycline, but not its antibiotic properties.

The Institute is pleased by the response that its program announcement, requesting research proposals on infectious causes of rheumatoid arthritis, has evoked. This year, a new approach has emerged for the study of this important area. For the first time, researchers have succeeded in genetically manipulating mice to carry a specific genetic trait that is closely associated with spinal

arthritis in man. The ability of infectious agents to induce arthritis in these mice is being evaluated.

Numerous Americans, largely young women, suffer from systemic lupus erythematosus (lupus), an inflammatory, immune-mediated disease that causes distinctive rashes, arthritis, and life-threatening kidney damage. Lupus is found much more frequently in women than in men (9 to 1) and affects more blacks than whites (3 to 1). Recent research indicates that different autoantibodies, antibodies that react against the body's own tissues, are closely related to specific clinical features of lupus. From sophisticated immunogenetic investigations, we are learning that immunologic abnormalities are frequently found in female relatives of lupus patients, thus providing valuable information about how the disease is genetically linked. Important questions remain regarding the epidemiology of lupus and the undiscovered factors that trigger the immunological defects. The Institute is also encouraging enhanced research on other major rheumatic diseases: arthritis of children in its many forms; Sjogren's syndrome; systemic sclerosis and other forms of scleroderma; and the spondyloarthropathies (arthritis of the spine).

Twenty-four million Americans are estimated to have osteoporosis, the leading cause of bone fractures, both in postmenopausal women and in the elderly in general. A major, long-term clinical trial supported by the NIAMS has shown that fluoride therapy to reduce the incidence of fractures in older women is not effective. Recent research, however, has indicated that physically active young women have more dense bone in the spine than do young women who are physically inactive; and this is encouraging in terms of developing a preventive strategy.

The NIAMS is sponsoring a scientific workshop on osteoporosis in February 1990 to enhance communication among investigators and speed research progress. The Institute is also collaborating with the World Health Organization and the National Institute on Aging to conduct important epidemiological studies on osteoporosis.

Osteoarthritis is the most common form of arthritis, affecting both the middle-aged and the elderly. It is thought to be caused by degenerative changes in the cartilage of joints. Recently, investigators employed a new microscopic computerized X-ray technique to detect the sequence of events leading to osteoarthritis; they found that the earliest changes occur in the bone that lies just beneath the cartilage. In other research, investigators are studying the interaction between porous-coated joint replacements and the surrounding bone tissue to enhance both the stability and longevity of joint replacements. In addition, a recent workshop discussed biologic restoration of joint surfaces using graft materials.

Paget's disease of bone is another chronic disease characterized by excessive resorption of bone and formation of new bone. This abnormal turnover results in bone that is dense but fragile, often leading to striking bone deformities, such as an enlarged skull or bowing of the legs. Research on bone cells in tissue culture has shown that as bone is resorbed, regulatory growth factors are released. These growth factors may prove to be important in developing new strategies for treatment.

Over 100 different conditions are included among the heritable connective tissue disorders. Their clinical impact ranges from mild to devastating disability, and even to death. Among them are osteogenesis imperfecta, Ehlers-Danlos syndrome, Marfan's syndrome, and epidermolysis bullosa. Modern molecular biology now makes it possible to gain better insights into how basic genetic defects lead to the specific clinical symptoms of each disease. The Institute has convened a major scientific workshop to be held in April 1990 to bring together leaders in this field and set future research priorities.

Reducing risk of injury is important to millions of Americans who participate in exercise programs and sports. The results of a recent workshop on the inflammation that is generated by sports-induced tissue injury will be published shortly. A program announcement based on the recommendations from this workshop will be issued to stimulate research in the fields of musculoskeletal fitness and sports medicine.

The contraction and relaxation of muscle is modulated through release and sequestration of calcium by channels that function within muscle cells. By exploiting recent advances in genetics and genetic engineering, investigators are learning more about the relationship between the structure of these channels and their function. The Institute has planned a workshop that will focus on the structure and function of the principal molecules of muscle cells.

We continue to make significant progress in addressing the many skin diseases that afflict Americans. Among these is epidermolysis bullosa (EB), a group of devastating blistering diseases. We are especially encouraged by the discovery of an inbred strain of alpine sheep that manifests the characteristics of one of the most severe forms of the disease. Use of this animal model will greatly facilitate research, including drug intervention studies.

In a FDA-sponsored clinical trial, phenytoin, an anticonvulsant, that had been reported to be promising for the treatment of EB, was shown not to be effective. We anticipate testing other candidate drugs on the patient population that is now being recruited by our National Epidermolysis Bullosa Registry. The registry will also identify separate populations that can be used to investigate the various forms of EB and delineate the causal mechanisms of these diseases more precisely.

Alopecia, which results in loss of hair, can be very debilitating psychologically. We have recently convened a scientific advisory group who recommended further studies on the basic biology of hair and its diseases. Recent improvements in organ culture techniques and the development of new animal systems to test drugs to combat hair loss make research in this area particularly promising.

The NIH Consensus Development Conference on Sunlight, Ultraviolet Radiation, and the Skin that we co-sponsored last May was a great success. Many recommendations related to human exposure to natural and artificial ultraviolet (UV) light emerged from the conference, as well as recommendations for further research, including immune dysfunction of skin by such exposure, intrinsic aging versus

photoaging of skin, and the potential role of retinoids in reversing the damage.

A scientific workshop on psoriasis recommended additional research on the molecular, immunologic, and pharmacologic aspects of this prevalent skin disease, and we are pursuing these approaches. Another area of research that seems to be particularly timely concerns wound healing. The recent development of "second skin" dressings and animal models with impaired wound healing, for example in the diabetic rat, will facilitate further progress in that area.

I am delighted to report to you the significant strides we have made in our Intramural Program. Effective January 1, 1990, we inaugurated the Laboratory of Skin Biology, whose primary mission is the conduct of basic research on skin. Moreover, our Orthopaedic Research Laboratory has been particularly productive this year and has rapidly become an integral part of the Institute's Intramural Program. Additional space has been made available to the Institute for the further development of the Intramural Research Program.

In an advance that may usher in a new era in the treatment of immune-mediated diseases, NIAMS intramural scientists have determined the complete structure of a key protein in humans involved in triggering allergic reactions. They are now focusing their research efforts on a search for drugs that will prevent allergy attacks. Other breakthrough research conducted in the Institute's Intramural Program demonstrated a defect in the neuroendocrine response to inflammation in an animal model of persistent arthritis. This could shed light on causal factors in rheumatoid arthritis and other rheumatic diseases.

In the field of AIDS-related research, Institute-supported researchers, utilizing a new biotechnology, have been able to detect minute quantities of human immunodeficiency virus (HIV) in skin biopsy tissue specimens. This can enhance the safety of skin grafting procedures. Other NIAMS-supported researchers have reported that zidovudine (AZT) can cause psoriasis to regress in HIV-infected individuals. This paves the way for a better understanding of the cause of psoriasis as it relates to the body's immune system.

Finally, I want to mention the comprehensive collaboration between the NIAMS and the Department of Defense to study skin, rheumatic, and musculoskeletal manifestations of disease in Army personnel who are HIV-positive. We foresee a synergism from which both agencies will benefit--as will the American people.

Mr. Chairman, the budget request for this Institute for Fiscal Year 1991 is $176,080,000. I will be pleased to answer any questions you may have.

SHULMAN, DR. LAWRENCE E.
Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases,
National Institutes of Health

July 25, 1919, Boston, Massachusetts

Education: Harvard University, A.B., 1941; Yale University Graduate School, Ph.D., 1945; Yale University School of Medicine, M.D., 1949.

Professional History: 1949-50, Intern, Medicine, The Johns Hopkins Hospital, Baltimore, Maryland. 1950-51, Ayerst, McKenna and Harrison Fellow in Endocrinology, The Johns Hopkins University School of Medicine. 1951-52, Vernon D. Lynch Fellow in Internal Medicine, The Johns Hopkins University School of Medicine. 1952-53, Assistant Resident, The Johns Hopkins Hospital. 1954-present, Physician, The Johns Hopkins Hospital. 1955-75, Director, Connective Tissue Division, Department of Medicine, The Johns Hopkins University School of Medicine. 1960-66, Physician-in-Charge, Arthritis Clinic, The Johns Hopkins Hospital. 1956-67, Physician-in-Charge, Connective Tissue Clinic, The Johns Hopkins Hospital. 1966-69, Physician-in-Chief, Division of Chronic and Community Medicine, The Baltimore City Hospitals, Baltimore, Maryland. 1970-73, Associate Professor of Medical Care and Hospitals, The Johns Hopkins University School of Hygiene and Public Health. 1964-present, Associate Professor of Medicine, The Johns Hopkins University School of Medicine. 1976-80, Acting Associate Director for Arthritis, Musculoskeletal, and Skin Diseases, National Institute of Arthritis, Metabolism, and Digestive Diseases. 1980-83, Associate Director, Arthritis, Musculoskeletal and Skin Diseases, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases. 1983-1986, Director, Division of Arthritis, Musculoskeletal, and Skin Diseases, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases. 1986, Acting Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases. 1987-present, Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases.

Professional Organizations: American Association for the Advancement of Science, American College of Physicians, American Federation for Clinical Research, American Rheumatism Association (President, 1974-75), American Society for Bone and Mineral Research, The Arthritis Foundation, Brazilian Society of Rheumatology, Carla Curzio Neapolitan Society, Lupus Foundation of America, New York Academy of Science, Pan American League Against Rheumatism (President, 1982-86), Society for Clinical Trials, Sydenham Society, Society for Investigative Dermatology.

Honors, Awards: Senior Investigator Award, The Arthritis Foundation, 1957-62. Pemberton Memorial Lecture, 1963. Fellow, American College of Physicians, 1967. Wallace R. Graham Memorial Lecture: Toronto, 1973. The Heberden Medal for Research in the Rheumatic Diseases, Heberden Society, London, 1975. Distinguished Service Award, The Arthritis Foundation, 1979. Honorary Member, Brazilian Society of Rheumatology, 1980. Honorary Member, Chilean Society of Rheumatology, 1981. Knowles Lecture: San Francisco, 1982. Honorary Member, Costa Rican Association of Rheumatology, 1984. Honorary Member, Australian Rheumatism Association, 1985. The Public Health

Service Superior Service Award, 1985. National Lupus Hall of Fame, 1986. Elected Master, American Rheumatism Association, 1987. Honorary Member, Swiss Society of Rheumatology, 1987.

NATIONAL PLAN

Mr. NATCHER. Thank you.

When we held our hearings last year we talked about a national research plan. When will this plan be ready?

Dr. SHULMAN. The whole plan will be ready in two to two and a half years from now. The whole organization of that plan has been prepared. As you know, I have been waiting for senior staff to help me develop the plan. I am very pleased to report to you and introduce to you a new member of our new institute; Dr. Michael Lockshin. Dr. Lockshin was a professor of medicine at Cornell New York Hospital, an outstanding professor of rheumatology, an expert in lupus. I am proud of the fact that we have been able to recruit such an outstanding person to our program.

He and I will co-chair this whole vital effort. We have a steering committee. We intend to have ten different task forces. We need a task force for each of the five fields of the institute, and we have five cross-cutting issues each of which needs a task force.

This national plan will be carried out with the steering committee and task forces over the next two to two and a half years. We also need to spread the cost of this endeavor, considering our financial condition, over three separate budgets, this year, then next year, and the following year.

Mr. NATCHER. Will the plan identify specific funding priorities among your many areas of research?

Dr. SHULMAN. The plan will be developed by a group of experts in each of the various fields. Each of those experts will come and tell us the current state of research and the needs for research in the future. The steering committee will review it all, and then pull it all together for us.

LYME DISEASE

Mr. NATCHER. Doctor, what has been the rate of increase in new cases of Lyme disease during the past year?

Dr. SHULMAN. I will have to get that for you for the record.

Mr. NATCHER. Fine.

[The information follows]

Lyme disease is the most prevalent tick-borne disease in the United States. More and more cases of Lyme disease are being identified each year. The Centers for Disease Control estimated the number of new cases of Lyme disease in 1988 to be over 5,000. Experts agree that this is an extremely conservative number.

This may mean that there is an increasing number of cases or that the disease is being diagnosed more often. In 1979, the disease had been reported in only 10 States; it has now been found in 43 States. At present, most of the cases occur in Connecticut, Massachusetts, Rhode Island, New York, New Jersey, Minnesota, Wisconsin, and California. The current increase in the tick population is closely linked to the deer population found in these States. For many years, the white-tailed deer population, the primary host of the adult tick, has been small. However, in recent years, the deer population has grown dramatically. As the deer population grows and spreads, so does the range of the deer tick.

Mr. NATCHER. Are most cases still concentrated in less than ten states?

Dr. SHULMAN. Most of the cases are concentrated in the Northeastern part of the country, the upper Midwest, and the Far West, although there are increasing numbers in other states as well.

Mr. NATCHER. When do you expect an early diagnostic test for Lyme disease to be widely available?

Dr. SHULMAN. We are going to have to review these new approaches, sir, as I outlined in my presentation to you, and then see which of these is the best for early Lyme disease.

Mr. NATCHER. Has there been any progress in the treatment of advanced cases of Lyme disease?

Dr. SHULMAN. Again, we need some clinical trials. No sir, to my knowledge there have been no further advances in this area, and we need clinical trials of various types, testing antibiotics and other approaches. Let me elaborate on the whole area of research on Lyme disease. You know that we and the Allergy Institute, after we put on a fine workshop, issued a joint request for applications for more research on the causes of Lyme disease.

A key question is; how much of the late manifestations of Lyme disease is due to the direct action of the bug itself, or how much is due to immune reactions to the bug? If the latter is true, for the late treatment of Lyme disease, antibiotics may not suffice. You may have to have immuno-therapy to treat immune reactions as well. We need trials to address this question.

RESEARCH PROJECT GRANTS

Mr. NATCHER. Your award rate is lower, as you know, than some of the other institutes, but so is your downward negotiation rate. In your view, Doctor, is it better to reduce the number of new grants and increase the size of each award?

Dr. SHULMAN. Mr. Natcher, you are asking a key question that you have asked of all of us here during these hearings. It is a terribly difficult and wrenching question. My personal view is as follows: let's say that we have downward negotiations of ten or twelve percent and we have an award rates of something on the order of one in five or one in six. This is our situation at the moment. If we eliminated all of the downward negotiations, we would then have to have an award rate of one in ten or one in 11. That would be disastrous, in terms of having people willing to participate in the research arena.

That is the dilemma that we are all in at the present time. I think all of us at NIH are, and will continue to be, wrestling with this particular question.

TREATMENT FOR ARTHRITIS

Mr. NATCHER. Doctor, I know of a case where a person has had an arthritic knee for many years. Every step, turn over in her sleep and she wakes up. Within the last two weeks she had a laser procedure, outpatient, and walked out the same day with no pain since that time.

Dr. SHULMAN. Would you be kind enough to give me the name of the physician?

Mr. NATCHER. He is in my home town. He won't be there long. He is an excellent physician. He will end up in Louisville or Nashville. He has a wonderful background.

I know the person that this procedure was performed on. Doctor, it has worked perfectly. What happens with this laser? How do they do that?

Dr. SHULMAN. Frankly, sir, I am not fully informed on this treatment, so, therefore, my question to you was a serious one.

Mr. NATCHER. I understand.

As I understand, Doctor, down my way—Kentucky, Tennessee—it is recent. It is almost what we would call brand new. I don't know whether they have it up here or not.

Dr. SHULMAN. What kind of arthritis did that person have?

Mr. NATCHER. I don't know. It was just an arthritic knee.

Dr. SHULMAN. There are many kinds. It is important to know. If this was an inflamed knee, it is quite possible that inflammation can be reduced by laser therapy.

Mr. NATCHER. Now, Doctor, in 1991 your new grants would receive a 21 percent average cost increase, as you know, yet there would still be 11.5 downward negotiation rate. Why are grant costs skyrocketing this way, Doctor. What is the reason for that?

Dr. SHULMAN. If you take a look at the average costs of our new grants, Mr. Chairman, actually, the average cost of our grants from 1987 on really has not gone up a great deal.

One of the reasons for this apparent estimate of '91 over 1990 is that the average cost in 1990 did not go up over that in 1989 at all. What the figures show is that the average cost of our competing grants in 1989 was $165,000 and in 1990, it is $167,000. Thus the average annual increase from 1989 to 1991 is 11 percent, the same as the average increase over the entire period since 1987.

Mr. NATCHER. Mr. Conte, I yield.

Mr. CONTE. Dr. Shulman, it is indeed a special pleasure for me to welcome you to our committee today. Your long and distinguished record in research and clinical excellence speaks for itself. You have a very fine crew over there, and you can bet your budget dollar the chairman and I and the rest of the committee will go the distance for you.

Arthritis is a crippling and devastating disease, which afflicts millions of Americans. Now, I hear a protein that blocks interleukin 1 has been found, which might be used for the future development of drugs. What is the status of research and this protein, what have you learned about the immune system and how it is involved in arthritis?

Dr. SHULMAN. That is a very interesting new development. This is called IL-1ra. It was developed by a new biotech firm in Boulder, Colorado, called Synergen Corporation, working in close contact with the Chief of the Department of Rheumatology at the University of Colorado in Denver, William Arend. This concerns cellular messengers called interleukins. Interleukin-1 is one of the cellular messengers that turns on both inflammation and collagenase, an enzyme that breaks down collagen. Therefore interleukin-1 is doing the damage to the joint. What they have found is a substance that blocks the receptor in the joint for interleukin-1. Their approach is extract from the human joint the substance that turns this whole system off, grow it up in the laboratory, produce it in large amounts, then we might be able to turn off the ability of interleukin-1 to promote inflammation.

The current status is that Synergen has entered into agreements with Hoffman LaRoche to evaluate this system in experimental animals. In the meantime, Dr. William Arend has submitted two applications to our institute in the interleukin-1 area. They have done well in competition. In spite of our low award rate, it is likely that they will be funded. This is a new development in research on rheumatoid arthritis.

OSTEOARTHRITIS

Mr. CONTE. Osteoarthritis is a major disease of the joints. Can you bring us up to date on what new knowledge has been gained about the biology of cartilage and the molecular changes associated with osteoarthritis?

Dr. SHULMAN. The cartilage consists mainly of type 2 collagen. Type 1 is in the skin; type 2 is in the cartilage. New collagens have been recently discovered. Type 9, particularly, has been found to play an important role as the glue for type 2 collagen.

In addition, interleukins seem to be playing a role in cartilage turnover. Interleukin-2 has been proposed as a measure of the activity of the turnover of cartilage.

Thirdly, in an experimental animal model of osteoarthritis, using a special type CT scan, it has been found that there are changes in the bone under the cartilage, even before any changes in the cartilage take place. This suggests that mechanical stress on the bone may in turn lead to cartilage degradation.

Mr. CONTE. I understand that changes in dietary fat can alter immune response and inflammatory reactions according to news reports. If one can understand how diet influences cell functions, could it be possible to devise novel ways to interfere with chronic inflammation and in tissue injury?

Dr. SHULMAN. Yes sir. As you know, there has been great interest in omega 3 fatty acids, fish oils, and what their anti-inflammatory properties may be. We have ongoing research in this area. Fish oils have even been used in experimental models of lupus to block the inflammation of kidneys in this disease. We have some notion that even olive oil may be protective, according to certain reports from Greece, but this is all very premature. I am not holding out too much promise for this approach, Mr. Conte.

MUSCULOSKELETAL DISORDERS IN THE ELDERLY

Mr. CONTE. How can senior citizens avoid the crippling effects of musculoskeletal disorders?

Dr. SHULMAN. There is a lot we could do for our senior citizens. We have talked about the importance of prevention of osteoporosis; this is terribly important. We also know that obesity is bad for one's knees. Keeping our weight down is very important.

Exercise in us older folks happens to be good. We are not running a great risk to our joints by exercising. Even marathon running in some of our senior citizens doesn't seem to be producing much damage. There is good work being done at Stanford University in this arena.

Mr. CONTE. If you have knees like mine, you are not able to run marathons.

Dr. SHULMAN. I am glad you are able to get around so well this year.

L-TRYPTOPHAN

Mr. CONTE. I don't know about this doctor down in Kentucky, maybe I ought to go down and see him. But I think my doctor at Johns Hopkins Hospital has done well in the new prosthesis of knees. I swear by it. I have no pain. I go hunting. He did a good job.

L-tryptophan has been in the news recently. I understand that severe muscle aches and tightening of the skin are caused by ingesting this compound. What can you tell us about this problem?

Is it something that we need to be more vigilant on? Or will this go away with tighter control of the health food industry?

Dr. SHULMAN. This is a new serious outbreak, an epidemic. The story began on October 30 when physicians reported three cases to the New Mexico Department of Health. These were people who had incapacitating muscle pain all over, and fever. They had large numbers of eosinophils, which are the red-spotted white cells in the blood. They comprised 50 percent, when you are only supposed to have five percent or less in the blood.

Many had coughing and shortness of breath. They then developed swelling of their extremities. They also had involvement of other parts of the body.

Within two weeks the New Mexico Department of Health had gathered 30 cases; they notified both the CDC and the FDA, and discovered that these people had all taken L-tryptophan. This is an essential amino acid used to build protein. People take this L-tryptophan, by purchasing it over the counter in health food stores, or doctors may prescribe it. It is thought to be a safe sleeping pill. It is also given for premenstrual tension, or anxiety; psychologists give it for depression.

The CDC notified the states. Within the next two months, cases were found in every state of the union, except for Alaska. As of the beginning of this year, there were over 1,000 cases reported. We now have publications appearing in the literature.

The first paper appeared this week in the AMA Journal. I am writing an editorial on this new disease called the eosinophilia myalgia syndrome (EMS) for another journal. The reason is that it produces an illness that is similar to a disease that I discovered 15 years ago called eosinophilic fasciitis. This came as a result of too much exercise.

We at NIH have formed a research group to study this in many ways. Much of the L-tryptophan has been traced to a single producer. It is thought that 80 percent of the L-tryptophan sold in this country comes from this producer.

Therefore, the question is, is it the L-tryptophan itself. People have been taking L-tryptophan for some time—why this explosive outbreak? Or is it due to a contaminant? There was a presumed contaminant in Spain—there was a toxic oil syndrome, which produced the same type of clinical picture like EMS. It was produced by adulterated cooking oil in a poor district outside Madrid. They had 20,000 cases and 318 deaths. There are already 15 deaths from

this epidemic of EMS; in part, due to neurological development where you may get an ascending paralysis.

SKIN DISEASE RESEARCH CENTERS

Mr. CONTE. Several years ago we established a program for skin disease research centers. What progress has been made and how much are you going for in the budget?

RESEARCH TRAINING

With the budget constraints and rising outside salaries, your institute is facing severe problems in getting scientists. What is the impact of holding the line on research training and manpower development programs?

Are you concerned that the pool of qualified young investigators might decrease in the decade ahead?

[The information follows:]

Maintaining a cadre of skilled scientific investigators is critical to the missions of the Institute. We are concerned about holding the line on research training and manpower development programs. The number of research trainees for FY 1991 will be supported at the same dollar level available in FY 1990. The FY 1991 request will support 52 research career development awards, a decrease of 1 award from FY 1990.

The current size of the pool of young investigators is insufficient in light of the numerous exciting research opportunities facing the Institute over the decade. The number of trainees had decreased significantly over the years, and the current levels are not sufficient to replace investigators that are being lost. Specifically, we need more young persons properly trained in the modern scientific methodologies of molecular and cell biology, where there is need to maintain the attractiveness of a career in biomedical research. Even more critical is an expansion in research career manpower awards, so that they can apply those techniques to all categorical interests of the Institute, including musculoskeletal fitness.

Dr. SHULMAN. In planning for the skin disease centers, we worked with all the leaders of skin diseases (dermatology) research four or five years ago. We sat with them to discuss the different types of centers. It turned out that the type of research center, called core centers, best fit their needs. Our plan was to start this center's program with six of these core skin disease research centers.

The funds recommended were for three centers from the Senate—without much of a contribution from your House committee, as you remember. So we split the difference, at two centers when the conference report came in. At that time, we were reducing centers by downward negotiations of 15 percent. That is where we are.

One center is at New York University and the other at Case Western Reserve at Cleveland. There were eight applications for those two centers. The plan is still for a total of six such centers when funds become available.

Mr. NATCHER. Your statement describes the discovery of an animal model for the skin disease EB. Will this substantially speed up the development of treatment for this particular disease?

EPIDERMOLYSIS BULLOSA

Dr. SHULMAN. We hope so, sir. The new development is a model, of the most severe form of EB. There are some 16 to 18 different

types of this disease, EB—epidermolysis bullosa. One of the worst types is called the recessive dystrophic form. DEBRA, which is the organization, speaks to dystrophic EB. This, the worst form of the disease, is replicated in alpine sheep grown in Switzerland. We hope that this will provide a very fine model for developing new treatments, sir.

Mr. NATCHER. What help can you offer these patients at this time, Doctor?

Dr. SHULMAN. We are looking for new approaches. I will tell you what we can do now. One of the forms is EB acquisita, which is an immune-mediated disease, different from the type we were just talking about. There are specific antibodies directed to skin proteins. It has been shown that cyclosporin-A, an immuno-suppressive drug, is helpful for this form of the disease.

Another possibility is whether or not collagenase causes the collagen defect in EB. It is on this basis that the drug phenotyoin, which is really Dilantin, a drug used to combat seizures, was used, because it had the power to block collagenase. Unfortunately, a trial has been conducted and it was found that phenotyoin was not effective for this serious form of the disease.

1990 OPERATING PLAN

Mr. NATCHER. Your final 1990 appropriations is about $1.6 million above your original request. Comparing this total with the original budget it appears you have shifted substantial amounts from extramural grants to overhead and in-house research. Why was that done, Doctor, and what impact did this have on the number of new projects which you can fund this year?

Dr. SHULMAN. It is a very complicated response that needs to be made. With your permission, I will provide it for the record. But at this time I will give you a direct response as to where that stands.

Mr. NATCHER. Go right ahead.

Dr. SHULMAN. Let me start from the beginning. We started off with a President's budget of $168,588,000. You added $3,000,000. We are grateful for that. The Senate agreed to that amount but gave slightly different directions as to how we should be expending those funds.

At any rate, when we started, at the conference, you and the Senate were only $15,000 apart for our institute. You split the difference and gave us generously $8,000 under those circumstances. So we ended out with $171,681,000.

Then we started to get our reductions. We had reductions from the salary cap, a procurement reduction, salary expenses reduction, and then a sequester of 1.35 percent, which brought us down to $168,930,000.

Then we had an extramural construction tap. We ended up with an actual working budget which has a little less than the President's budget. Therefore, our $3 million that we expected to have above the President's budget is gone.

Now, when we started to plan for this, the Senate said, Mr. Natcher, that we should use a significant part of the increase for the development of our intramural program. We had an unusual opportunity for our intramural program. We have a small intramu-

ral program. We started off with an intramural program that is a little over five percent of our total budget, whereas the average at NIH is 11 to 12 percent of the budget.

We were at this time given by the decision-makers, the people in the Office of the Director, Dr. Raub and Dr. Wyngaarden we were kindly given 8,000 additional square feet to begin to develop our intramural program, as was requested by the Congress.

So we began to implement, with the direction of the Senate, the development of our intramural program. First was the development of an orthopaedic research program. We have also added a skin biology research program, according to suggestions from our advisors.

If we take a look at the training side, you will see the training increased by $758,000. Well, that was to correct the disproportionately low figure of 194 training slots and to bring it up to 225 training slots, to redress the training issue.

In the case of our own research, management, and support, we were, and still are, a lean administrative outfit. We had to bring on certain additional people to meet our responsibilities. Dr. Lockshin and his support person had to be brought on board. Things were exploding in terms of bone diseases research and osteoporosis. We had Dr. Gordon managing everything in that arena, and he needed help. We recruited Dr. Joan McGowan, another fine addition to our staff, to manage the bone diseases and bone biology program.

We also needed help in the grants management area, because we were understaffed there. In addition, there were increases in salaries that were unexpected.

What it all came down to in terms of the number of competing grants, we had planned in the President's budget for FY 1990 to have 131 new and competing grants. We ended up with 135 new and competing grants this year.

Mr. NATCHER. Thank you, Dr. Shulman.

When we get the transcript back you can put in a full statement in answer to that question.

[The information follows:]

The increase in the Research Management and Support is required for several reasons. As stated, a portion of the increased costs is associated with the development of the National Plan and the addition of an Institute Deputy Director and support person. The Institute also needs additional staff support for the epidemiology program and the clinical trails program. Further, urgently needed additional space for the extramural program will be made available by NIH in FY 1991. This space will require some renovation to accommodate our extramural program and will result in an approximate three-fold increase in our overhead costs.

Mr. NATCHER. Dr. Shulman, it is a pleasure to have you before our committee. We want to thank you and your associates for appearing at this time on behalf of your budget request for the fiscal year 1991.

Dr. Raub, the hearings have all been good. I say that to you frankly. We appreciate it.

We will now adjourn until 2 o'clock Monday afternoon.

[The following additional questions were submitted to be answered for the record and the justifications follow:]

INTRAMURAL RESEARCH

Mr. Natcher. If your budget request for FY 1991 is approved, funding for in-house research will have increased by 33 percent from FY 1989 to FY 1991. What is your eventual target for the size of this program?

Dr. Shulman. In FY 1989, the intramural research program constituted only 5 percent of the Institute budget. The NIH has allocated 8,000 square feet to accommodate the development of the intramural research program. This space will be available to the NIAMS in phases during FY 1991 and FY 1992, and it will allow us to implement some of the recommendations contained in the long-range plan for the intramural program forwarded to the Congress in February 1988. In that plan, a number of scientific and clinical areas were identified as unique opportunities for future expansion. An increase in the number of senior investigators will be required in the Laboratory of Physical Biology, the Laboratory of Structural Biology Research, and the Laboratory of Skin Biology. Also a new Laboratory of Bone and Connective Tissue Biology will be established to complement the Orthopaedic Program.

A specific target size was not identified in the plan, nor was a timetable set for the enhancement of the program. Currently, the NIAMS Intramural Program represents about 5 to 6 percent of the Institute. The average intramural program at the NIH is in the 10 to 12 percent range. We are aiming for the later proportion for the NIAMS intramural program eventually.

RESEARCH CENTERS

Mr. Natcher. The share of your total funding going to research centers is higher than the NIH average. Is the center mechanism particularly useful in your fields of research?

Dr. Shulman. Yes, the centers program is particularly important to our Institute. Many of the diseases under the purview of the Institute are chronic diseases, and it is important to examine many diverse aspects with respect to them. In addition to basic studies of the underlying mechanism of disease, research centers provide a mechanism for carrying out studies in prevention, therapy, and rehabilitation. The NIAMS centers do not replace individual research efforts; but they supplement an ongoing research base of excellence and provide unique opportunities for motivated researchers to pursue research related to arthritis and musculoskeletal and skin diseases. Three kinds of centers are supported by the NIAMS: Multipurpose Arthritis and Musculoskeletal Diseases Centers, Specialized Centers of Research, and Skin Diseases Research Centers. Each type of center contributes a unique thrust not available through other research mechanisms.

Multipurpose Arthritis and Musculoskeletal Diseases Centers are comprehensive centers requiring an excellent research base and comprehensive patient and professional education programs. These centers support core facilities, innovative developmental and feasibility projects, and inventive studies on epidemiology, education, and health services research. Research core units provide

technical services to a number of investigators, with economy and quality control not readily achievable on a smaller scale. A tissue culture facility is an example of a research core unit. Developmental and feasibility projects explore new and innovative research ideas for up to 3 years. This seed money allows investigators to establish the research base for a larger program. Studies in epidemiology, education, and health services research serve the unique role of translating basic research into clinical practice, and they provide the tools with which patients and health professionals can deal with these debilitating diseases.

Specialized Centers of Research are established in the fields of rheumatoid arthritis, osteoarthritis, and osteoporosis. This type of center brings together senior researchers from a variety of backgrounds to conduct separate and collaborative basic and clinical research projects on diseases of national importance. The goal is a more rapid progress in a defined disease.

Skin Diseases Research Centers are awarded to an institution with a research base of excellence in skin diseases. The grant supports core facilities and developmental and feasibility studies. It fosters important research interactions and provides seed money for young or established investigators to pursue innovative research leads.

Mr. Natcher. Do you plan to increase the number of Skin Diseases Research Centers in FY 1991?

Dr. Shulman. The FY 1991 budget does not allow expansion of the NIAMS Centers Program to include more Skin Disease Research Centers. The eventual expansion of the Skin Disease Research Centers from the current two centers to six centers is the first priority for the Centers Program.

RESEARCH MANAGEMENT AND SUPPORT

Mr. Natcher. Your request for Research Management and Support increases by almost 14 percent. Aside from developing the national research plan and adding two staff people, what else would this large increase be used for?

Dr. Shulman. The increase in Research Management and Support is required for several reasons. A portion of the increase costs is associated with the development of the National Plan and recruitment of an Institute Deputy Director and support person. The Institute also needs additional staff support for the epidemiology and clinical trials programs. Further, urgently needed additional space for the extramural program will be made available by NIH in FY 1991. This space will require some renovation, and it will result in an increase in our overhead costs.

PREVENTION EDUCATION ACTIVITIES

Mr. Natcher. How much are you budgeting for prevention education activities in areas such as low back pain, exposure to sunlight, and osteoporosis?

Dr. Shulman. A significant portion of the efforts of the Office of Prevention, Epidemiology, and Clinical Applications; the Office of Scientific and Health Communications; and the National Arthritis and Musculoskeletal and Skin Diseases Information Clearinghouse involve providing information about prevention of specific diseases, such as low back pain, osteoporosis, Lyme disease, and overexposure to ultraviolet sunlight, as well as prevention of disability from other diseases, such as arthritis and systemic lupus erythematosus. We have developed special information packages in these areas for the public, and bibliographies have been prepared on several of these topics for health professionals. These activities account for about 20 percent of our Research Management and Support budget and about 10 percent of our R&D Contract budget.

Initiatives in osteoporosis include a booklet based on the Director's "Medicine for the Layman" presentation, radio and television interviews, and news stories on major findings and the recent scientific workshop. We would like to mount additional efforts in this area, including, for example, collaboration with the National Osteoporosis Foundation and the Arthritis Foundation to plan, develop, and promote preventive interventions for osteoporosis and work with the food industry to reach consumers with information about recommended levels of calcium intake and its bioavalability.

In the area of Lyme disease, we have several ongoing efforts and projects. Last May, we sponsored Dr. Anita Curran (formerly Commissioner of Health of Westchester County, New York) in an NIH Prevention Seminar on Lyme disease. Last July, Institute staff participated at a congressional briefing and press conference on Lyme disease in anticipation of Lyme Disease Awareness Week. We are collaborating with the NIAID and the Centers for Disease Control on a brochure on Lyme disease for the public and with the NIAID on a wall chart on diagnosis of Lyme disease for physicians.

One of our goals in lupus is to improve the patient outcomes in high-risk populations and to prevent complications and premature death and disability. The prevalence of lupus among black females is about nine times that in white females. There are indications that black females do not have as ready access to health care as white females, and they may not be getting available treatments for lupus early in their disease. We are developing materials for community organizations that reach black women ages 12 to 44 and a slide program for health professionals that address these issues. We are also creating new major bliographies on systemic lupus erythematosus for health professionals.

SKIN GRAFTS

Mr. Natcher. You mention the finding that the AIDS virus can be transmitted through skin grafts. Is this something we should be concerned about?

Dr. Shulman. Although the AIDS virus could be transmitted through donated human skin grafts, most skin grafts are autografts; that is, the skin graft tissue is harvested from one site for transplantation to another site on the same individual. Therefore, the frequency of transmission is likely to be low. Additional research is needed to determine the level of risk.

We still need to be concerned about HIV transmission through grafts because: (1) The consequences of HIV infection are very serious; (2) Blood screening for antibodies against the AIDS virus in skin graft donors could potentially miss early cases of HIV infection. After infection, it may take up to 2 years to develop detectable antibodies against the virus; and (3) there is likely to be a delay of up to several years before the full extent of transmission of the AIDS virus from unscreened skin graft tissue is known.

The adaptation of the polymerase chain reaction technique for detecting minute quantities of genetic material from the AIDS virus in skin graft tissue is likely to help identify AIDS virus-infected skin tissue. This advance should have implications for a variety of other transplants, as well.

PREVENTION OF BALDNESS

Mr. Natcher. We hear many advertising claims about the effectiveness of the drug minoxidil in preventing baldness. What does the research actually show about the usefulness of this drug?

Dr. Shulman. Minoxidil is a medication, approved by the Food and Drug Administration (FDA) for treatment of male pattern baldness. Research upon which FDA approval is based, demonstrated that in areas treated with minoxidil there was a statistically significant increase in the number of hairs in patients when considered as a group. Not all subjects responded with hair growth; and of those that did, only a minority had cosmetically useful hair regrowth. The drug was found to be relatively safe. Only local irritation or allergy was noted at the 2 percent concentration that was approved by the FDA.

A number of other potentially useful drugs are under investigation, and one or more of these may prove to be more successful than minoxidil in prevention or reversal of male pattern baldness or in treatment of other diseases characterized by loss of hair.

SPACE MEDICINE

Mr. Natcher. Is your Institute becoming involved in space medicine issues, for example, in the areas of bone loss?

Dr. Shulman. The NIAMS is involved in several activities related to space medicine. Prolonged weightlessness causes both loss

of bone and loss of muscle mass. This is true, in spite of efforts to combat such a loss by exercise (for example, isometric activities). Much research, supported by the NIAMS, on the use and disuse of bone and muscle is applicable to research in space medicine.

NIAMS staff have been serving on NASA advisory committees to help share the knowledge gained in areas of common interest. Furthermore, the NIAMS and the NASA are together planning a research workshop to promote further scientific investigations in these two areas. The goals will be to enhance research on earth that may help space travelers and to conduct research in space that may be of special relevance to weight-dependent biological and physiological processes on earth.

Mr. Natcher. How may clinical trials are included in your FY 1991 request, and at what funding level?

Dr. Shulman. In FY 1991 we hope to fund 29 clinical trials at a funding level of $9.150 million. This includes clinical research supported through research project grants and R&D contracts. The greatest proportion of clinical trials are supported by the grant mechanism.

Mr. Natcher. Identify how many research centers you have, according to disease area.

Dr. Shulman. Currently we have nine Specialized Centers of Research consisting of three—in osteoarthritis, three in osteoporosis, and three in rheumatoid arthritis; 14 Multipurpose Arthritis and Musculoskeletal Disease Centers, and two Skin Diseases Research Centers.

Mr. Natcher. How much funding is included in the FY 1991 request for the Epidermolysis Bullosa Patient Registry?

Dr. Shulman. For FY 1991, we are estimating the funding level to be $680,000.

Mr. Natcher. Provide an estimate of the research funding allocated in FY 1989 - FY 1991 to the following diseases: lupus, arthritis, Lyme disease, epidermolysis bullosa, and osteoporosis.

Dr. Shulman. The following table reflects the funding in thousands for these diseases:

Disease Area	FY 1989	FY 1990	FY 1991
Lupus	$11,843	$12,969	$13,609
Arthritis	71,423	74,047	76,420
Lyme Disease	788	2,571	2,703
Epidermolysis Bullosa	3,942	4,228	4,393
Osteoporosis	10,965	11,300	11,735

POTENTIAL TREATMENTS

Mr. Roybal. What are the potential treatments for osteoporosis in older adults?

Dr. Shulman. There are two important approaches to the treatment of osteoporosis in older adults: treatments that restore lost bone and those that prevent further bone loss. Restoring lost bone is the more challenging area. Several of the more promising treatment modalities discussed at the recent meeting, Research Advances in Osteoporosis are as follows:

Estrogen replacement at the time of menopause prevents accelerated postmenopausal bone loss and reduces the risk of fracture of the hip, spine and distal radius. The earlier treatment is begun, the better the outcome, but some benefit may be realized up to 10-15 years after menopause. A multi-center clinical trial, the Postmenopausal Estrogen/Progestin Intervention study (PEPI), is now in progress supported by the National Institutes of Health (NHLBI, NIA, NIAMS, NIDDK) to assess both the bone-related and cardiovascular benefits of combinations of these hormones.

Recent and ongoing studies suggest potential efficacy for the bisphosphonates, analogs of pyrophosphate, both in treating established osteoporosis (restoring bone mass previously lost) and in prophylaxis (preventing bone loss). In addition, they may play a role in intermittent combination therapy programs with other agents. These potentially useful experimental compounds are simple to administer (oral), relatively inexpensive, and safe (when used intermittently).

Calcitonin, administered by injection, has been shown to decrease bone turnover and increase body calcium and bone mass. The recent development of a calcitonin preparation effectively administered by nasal spray will facilitate the necessary clinical trials to assess the long-term efficacy of calcitonin.

Calcium supplementation, when dietary sources are inadequate, is a recommended adjunctive treatment in postmenopausal women and the elderly. Calcium intake is especially important during the period of peak bone mass attainment, but factors other than calcium predominate during the menopausal transition in women. However, recent studies do indicate a positive effect of high calcium intake in older adults, and a level of 1,000 to 1,500 mg per day is recommended.

Treatment with Vitamin D analogs can be important in the elderly in whom low stores of the vitamin are common. Vitamin D deficiency impairs calcium absorption, and this may adversely affect bone remodeling and contribute to bone fragility.

While weight-bearing physical activity is necessary for optimal bone health, the effectiveness of exercise as a treatment for osteoporosis has not been fully established. However, it does offer the potential benefit of slowing bone loss and may improve coordination, balance and muscle strength, thereby decreasing the likelihood of fracture, independent of bone mass.

A cautionary note has been struck by the recently completed trial of sodium fluoride, supported by the NIAMS. Sodium fluoride is unique in its capacity to promote increases in bone mass. It has been considered a very promising treatment for osteoporosis, and it is commonly used in many European countries. The controlled, prospective, randomized, clinical trials of the efficacy of sodium fluoride in reducing fracture rate have indicated that although this agent increases bone mass, it does not reduce fracture rate. These studies indicate the necessity for conducting careful clinical trials before adopting promising new treatments.

HEALTH CARE BURDENS

Mr. Roybal. Which treatment would reduce health care burdens?

Dr. Shulman. In order to reduce health care burdens, as well as pain and disability, treatments are needed that reduce fractures. In older adults, this means restoring lost bone and decreasing bone fragility. As indicated above, many of the current treatments are still experimental with as yet unproven long-term efficacy.

OSTEOPOROSIS AWARD RATE

Mr. Roybal. What is the award rate at the NIAMS with respect to osteoporosis?

Dr. Shulman. In FY 1989, 44 applications related to osteoporosis were approved for funding, and 14 of these were awarded. Thus, the award rate was about 32 percent. Total support for osteoporosis in FY 1989 was $10.965 million.

Mr. Roybal. How much funding would be needed to expand the areas of research to 50 percent and 100 percent?

Dr. Shulman. At the current 12 percent rate of downward negotiations, an additional $5.0 million would have been required to fund all approved applications. Half the applications could have been funded with an additional $1.3 million. However, the NIAMS would not ordinarily consider funding research on one disease at a payline significantly different from the general payline for the Institute. This would be detrimental to review system that identifies the highest quality research opportunities.

Mr. Roybal. Does additional research need to be conducted on osteoporosis? Can you describe what general areas of research the NIAMS is currently conducting? What federal resources would be needed to conduct such research?

Dr. Shulman. A great deal more research needs to be carried out, in order to be able to both prevent osteoporosis and treat already existing disease. General research area are given below. Estimates for research in these areas is not available.

Epidemiology and Pathogenesis. NIAMS-supported research is directed toward elucidating major genetic and environmental factors that affect the seemingly, inexorable loss of bone from the menopause and aging.

Prevention and Treatment. Major areas of research in prevention involve the role of calcium and exercise in building peak bone mass, as well as the effectiveness of estrogen in preventing postmenopausal bone loss. NIAMS-supported clinical trials are currently investigating:

- o effectiveness of different forms of calcium supplementation
- o combination of exercise, calcium and estrogen in post-menopausal women
- o calcitonin treatment for patients on glucocorticoid therapy
- o estrogen and progestin replacement therapy (Postmenopausal Estrogen/Progestin Intervention (PEPI) multi-institute study)

Risk Assessment and Clinical Evaluation. To identify persons at risk for developing osteoporotic fractures, a safe, simple, reliable, and low-cost method to determine bone mass is needed. In the last several years, progress has been rapid in new instrumentation for measuring bone mass. Research is directed toward determining the accuracy and precision, as well as the specific utility, of each of the major methods currently in use.

Basic Bone Biology and Structure. Bone formation and breakdown is regulated by a complex interplay of bone cells and factors that regulate the growth and function of the cells. Studies are in progress that use the techniques of modern molecular and cellular biology to describe and manipulate both bone-forming (osteoblast) and bone-resorbing (osteoclast) cells. Bone cells both produce and store a number of well known growth factors. NIAMS grantees are investigating the roles of insulin-like growth factors (IGF-I and IGF-II), interleukin 1 (IL-1), tumor necrosis factor (TNF) and transforming growth factor-beta (TGF-beta) in bone biology. Some evidence suggests that TGF-beta may serve as a coupling factor to link bone breakdown to bone formation.

The particular structural configuration of bone contributes to its strength and resistance to fracture. Ongoing studies are elucidating the effect of a variety of factors, including mechanical loading, on the structure and strength of bone.

APPROVED APPLICATIONS

Mr. Roybal. How many applications in the area of osteoporosis have been approved by the NIH study sections? How many applications have been funded? How many applications are you unable to fund because of limited resources?

Dr. Shulman. There were 44 applications approved for funding in 1989. Fourteen projects were funded. Thirty applications approved for funding could not be funded.

RETAINING INVESTIGATORS

Mr. Roybal. At the rate of current funding can you retain established scientists and attract new researchers to the field of osteoporosis?

Dr. Shulman. Fiscal restraints prevent funding many highly promising projects by both established and new investigators.

COLLABORATIVE EFFORTS

Mr. Roybal. Can you describe the collaborative efforts among the NIH Institutes regarding osteoporosis?

Dr. Shulman. The NIAMS both leads the effort, and collaborates and cooperates with several other funding components of the National Institutes of Health to support research, as well as public and professional education, in the area of osteoporosis. This is accomplished by using joint Program Announcements and Requests for Applications and by jointly funding some large and expensive projects.

In 1987, the NIAMS, NIA, and NIDDK issued a joint Request for Applications to fund Programs of Excellence in Osteoporosis. Three of these programs were funded in FY 1987, one supported by each of the sponsoring institutes. In 1989, the NIAMS and NIA used a joint Program Announcement soliciting applications to investigate the underlying causes of Type II Osteoporosis in men and women. In addition, the NIAMS and NIA are jointly funding a large multi-center study on the Risk of Hip and Colles' Fractures.

Four of the institutes (NHLBI, NIA, NIAMS and NIDDK) are supporting a clinical trial to determine the safety and efficacy of estrogen and progestin replacement. This study, Postmenopausal Estrogen/Progestin Intervention (PEPI) Study, will measure both bone-related and cardiovascular effects of hormone replacement therapy.

The NIAMS and the other institutes also cooperate in the sponsorship of national meetings on osteoporosis such as the recent workshop on Research Advances in Osteoporosis held February 26-28, 1990.

HEALTH CARE NEEDS

Mr. Roybal. What impact does osteoporosis have on long-term care needs of older adults? What is the impact of osteoporosis in older adults on health care needs and costs?

Dr. Shulman. The medical and social consequences of its associated fractures make osteoporosis a tremendous public health problem. At least 1.3 million fractures per year in the United States are attributed to the disease. The skeletal site most affected is the spine and, overall, almost a third of women age 65 years and over will have one or more vertebral fractures. Osteoporosis is responsible for over 90 percent of hip fractures and 75 percent of Colles' fractures in adults, along with a third of all other limb fractures. The lifetime risk of a hip fracture is -

15 percent in white women and 5 percent in men (equivalent to the combined lifetime risk of breast, uterine and ovarian cancer in women and about the same lifetime risk as prostate cancer in men.)

Costs are great, since a fourth of all patients with limb fracture require hospitalization, especially hip fractures. Hip fractures often lead to institutionalization; as many as 8 percent of all nursing home residents have had a hip fracture. The cost of acute and long-term care for hip fractures was estimated to be $7.3 billion in the United States in 1984. The cost of care for Colles' fractures in adults may reach $140 million each year.

Among women 50 years of age and over, new vertebral fractures are nearly three times as frequent as are hip fractures, with as many as 500 thousand women newly affected by vertebral fractures each year. Only a fraction of these patients are medically attended. Nonetheless, vertebral fractures in patients age 45 years and older account for 161 thousand physician office visits each year and over 5 million restricted activity days.

These figures will only worsen in the future as the population ages. By the year 2050, people over 65 years of age will make up 22 percent of the population, while those over 85 will comprise 5 percent. Between 1988 and 2050, the actual number of individuals age 65 years and over will increase from 30 to 67 million in the United States (U.S. Bureau of the Census 1984). The incidence of osteoporosis-related fractures rises exponentially with age. It has been estimated that there would be 350 thousand hip fractures annually in just 30 years, at a cost between $31 and $62 billion each year.

Mr. Roybal. What is the NIAMS doing in reference to educating health professionals and the public about osteoporosis? Do you envision that there are more opportunities to inform the public through a resource mechanism in the private sector?

Dr. Shulman. The NIAMS has been involved in several education and information activities in osteoporosis for health professionals and the public. The Institute has sponsored major, state-of-the-art conferences on osteoporosis, in 1984, 1987 and 1990. These attracted hundreds of physicians, and the proceedings have been published in medical journals and promoted via specialized media to health professionals, as well as to the public.

The National Arthritis and Musculoskeletal and Skin Diseases Information Clearinghouse provides a key role in collecting published and audiovisual information about osteoporosis. This is maintained on a public database available and promoted to physicians, allied health professionals, health educators and medical librarians. The Clearinghouse also produced, with review by leading experts, two major annotated bibliographies on osteoporosis, which assist health professionals in their continuing education on the disease and in patient education about it.

Both the Clearinghouse and the Institute's public affairs staff spend considerable time responding to public inquiries about osteoporosis; it is among the most popular topics among about

20 thousand total inquiries received yearly. We have compiled an information package to assist with these inquiries that consists of major review articles and lay summaries of these articles.

In addition, the Institute has a detailed booklet on osteoporosis (some 100 thousand have been distributed), a flyer produced with a nonprofit association for grocery stores nationwide (some 20 thousand have been distributed in 1,500 locations), and most recently, a reprint of a booklet based on a Medicine for the Layman presentation by the Director. We continue to provide speakers for meetings, do radio and television interviews, and prepare research news stories from conferences and major journal articles.

Osteoporosis is such a common disorder, with at least 24 million women in the U.S. afflicted, and so many more people could benefit from information on its prevention (particularly all females from childhood to the age of menopause) that a large effort involving many organizations, groups, and individuals is essential to effectively inform these women and the health professionals that serve them. Even if there were a large infusion of funds for the NIAMS to lead such an effort, we would involve the private sector to work closely with us in the planning, and they would be key to carrying it out.

There are already many ongoing efforts to inform the public about osteoporosis in the private sector. These include most impressive efforts by the National Osteoporosis Foundation, which has published several materials for the public and health professionals and which leads and coordinates Osteoporosis Prevention Week each May, and similar efforts by the Arthritis Foundation. A large array of both for-profit and nonprofit organizations also are involved in conducting information and education activities in osteoporosis, from pharmaceutical and dairy concerns to professional groups to the Girl Scouts and the YWCA. Certainly the private sector does and should play an important role in osteoporosis information and education.

SYSTEMIC LUPUS ERYTHEMATOSUS

Mr. Stokes. Please bring me up-to-date on your lupus research program. As you know, the Congress encouraged the NIAMS to expand its efforts in this area.

Dr. Shulman. Research on systemic lupus erythematosus continues to be a major focus of research both in the extramural program and the intramural program. Survival has improved. Lupus has become better recognized, and diagnostic tests, such as antibody to DNA and Sm antigen and serum complement components, are providing important markers that allow physicians to target management of the disease to the individual patient. Focus is now on helping the patient live a more normal life.

There is currently a great deal of research on lupus, with many different projects on immunology and genetics of lupus, and on experimental therapies. Advances recently reported include new studies regarding the relative safety of pregnancy in SLE patients, methods to reduce miscarriages, and better outcomes for patients with lupus kidney disease. Through research we now have a better understanding of the genetic abnormalities that make persons

susceptible to lupus, but many questions remain. Work in progress is concerned with the unusual racial and sex distributions of this disease.

In FY 1989 the NIAMS supported $12.969 million in research on lupus. NIAMS will also, in the future, host a scientific workshop on research opportunities in lupus.

OSTEOPOROSIS AFFECTS BLACKS

Mr. Stokes. To what extend does osteoporosis affect blacks? What types of studies are you conducting in this area?

Dr. Shulman. Hip fractures (typically a consequence of osteoporosis) are twice as common in whites as compared to blacks. There are about 75 thousand hip fractures each year in blacks. There are few data on the comparative incidence of other fractures related to osteoporosis in blacks. Large epidemiologic studies on osteoporosis in blacks have recently been funded by the NIAMS. Basic science projects are underway to help explain the black/white differences related to osteoporosis. In one interesting study, blacks were shown to have a lower rate of bone remodelling, which may explain the difference in bone mass between blacks and whites.

RESEARCH PROJECT GRANTS

Mr. Early. Doctor, how many new and competing grants will you be able to fund with the FY 1991 budget request?

Dr. Shulman. The NIAMS will be able to fund 150 new and competing grants at a cost of $30.4 million.

Mr. Early. How does this compare to the number funded in FY 1990 and FY 1989?

Dr. Shulman. For FY 1990 the Institute plans to fund 135 new and competing research project grants at a cost of $22.5 million. For FY 1989 the Institute awarded 185 new and competing research project grants at a cost of $30.5 million.

Mr. Early. What will the payline percentile be in FY 1991, and how does that compare to FY 1990 and FY 1989? Is it possible to give us some idea of what that would be in terms of priority scales?

Dr. Shulman. The percentile payline for FY 1991 will be 14.0. This compares to 14.0 for FY 1990 and 20.7 for FY 1989. Although there is no direct correlation between paylines and percentiles, it is estimated that a FY 1991 percentile payline of 14.0 is equal to a priority score payline of about 140.

Mr. Early. What percentage of approved grants would be funded under the budget request and how does this compare to previous years?

Dr. Shulman. For FY 1991 the NIAMS plans to fund 19.3 percent of the approved research project grant applications. This compares with award rates of 18.5 percent for FY 1990 and 28.2 percent for FY 1989.

Mr. Early. How does this compare to 1986-87, the year your institute was established?

Dr. Shulman. This compares with an award rate of 30.8 percent for FY 1987 and 33.1 percent for FY 1986.

SCIENTIFIC VIEWPOINT

Mr. Early. Doctor, a coalition of professional and voluntary organizations concerned with the programs of your Institute recommended a $50 million increase in the President's budget request Doctor, from a scientific viewpoint, could that additional amount be effectively spent on high quality research?

Dr. Shulman. Undoubtedly, this money could be spent on high quality research. The NIAMS could fund 63 more research project grants, 4 more core research centers on skin diseases, 30 more research career grants, 60 more research training positions, and 10 research contracts for clinical trials; and for adding connective tissue research to our intramural research program. This funding would permit a payline at the 21st percentile. It would provide funding for high quality research proposals in our various fields. Equally important, funding of career and research training positions would help us reverse the continuing downward trend of entrants into biomedical research.

Mr. Early. What research grant opportunities could the NIAMS support if additional resources were available?

Dr. Shulman. The NIAMS supports research in a broad range of debilitating diseases. These diseases include the many forms of arthritis, diseases of the musculoskeletal system, and diseases of the skin. The NIAMS also supports research in normal structure and function of the muscles, bones, and skin, including musculoskeletal exercise physiology. Some of the research priorities that would be funded if additional resources were available are described below.

Lyme disease. Lyme disease is a problem of increasing incidence as well as national and international importance and concern. Research is vitally needed to discover the precise mechanisms by which the infectious agent produces damage to different parts of the body. Although the disease responds well when treated early, many puzzles and problems complicate diagnosis and treatment. The symptoms vary widely between patients, antibody tests are unreliable early in the disease, some people produce no detectable antibodies, the organism is difficult to isolate from tissues, and the course of the disease is unpredictable. Especially needed are better treatments for late occurring chronic skin and joint disease, and neurologic and cardiac complications. Together with the NIAID, the NIAMS sponsored a scientific workshop on Lyme disease in December 1988, and as a result, issued program announcements and a request for applications. This year, the NIAMS is funding five new grants, and additional approved applications are pending.

Systemic lupus erythematosus. Systemic lupus erythematosus is a serious disease of unknown cause. Treatments are at best only partially effective. Current research focuses on a variety of

immunological and genetic abnormalities that characterize lupus and on potential viral causes for the illness. Many key questions concerning lupus remain unanswered and could be addressed by additional research: Why is lupus nine times more common in women than in men and three times more common in blacks than in whites? Why does lupus begin mostly in young people? Does it run in families; and if so, is it inherited? What are the basic immunologic defects in lupus, and how do these defects cause damage to the organs of the body? What are the initiating factors that trigger these immunologic defects? To address and answer these important questions, a much more intensive research effort is needed. Consequently, the NIAMS plans to hold a Workshop on Research Opportunities in Lupus in an effort to stimulate new epidemiologic, clinical, and basic science approaches. Funding of treatment trials could also be considered.

Rheumatoid arthritis. Research on this serious, crippling illness focuses on mechanisms of joint destruction, genetics, and treatment. NIAMS-supported centers also examine epidemiologic and psychosocial components of disease, including features associated with development of disability and effectiveness of exercise programs for rehabilitation. Rheumatoid arthritis is frequently accompanied by inflammation that leads to irreversible joint destruction and loss of function. Additional research is needed to unravel mechanisms involved in generation and maintenance of inflammatory processes within joints and to identify factors that predispose to development of the disease. A recent workshop brought together basic scientists studying chemical and cellular components of the immune system and clinical investigators studying the association of genetically determined cell markers and susceptibility to rheumatic diseases. This interaction stimulated the formulation of number of important research questions on rheumatoid arthritis. The effort to discover and apply effective therapeutic modalities to arrest and prevent joint damage in rheumatoid arthritis has been hampered by the limited number of clinical trials on rheumatoid arthritis. Additional resources could be used to expand support for clinical research.

Arthritis in children. Arthritis affects an estimated 200 thousand children in the United States. The NIAMS currently supports research to define genetic markers and factors that trigger the onset of pediatric rheumatic diseases and to determine why differences exist between pediatric and adult rheumatic diseases. Maturation of immune responses is suspected to play a role in arthritis. Because children have not been exposed to as many external antigens as adults, the search for immunologic clues in arthritis should be more straightforward in children. Furthermore, the hormonal environment in children differs from that of adults, and it is important to study the influence of these differences on the expression of immunity and inflammation. Because children are growing, their cartilage, bone, and other structural elements are under continuous remodeling. Detailed studies of the influences of growth on the destructive aspects of inflammation may provide new approaches to modifying the inflammatory process.

Spondyloarthropathies. This group of illnesses primarily affects young men. Research is needed to understand the striking association between these diseases and the specific genetic tissue

type, HLA-B27, still largely a mystery some 15 years after its discovery. It is not clear whether this is the major genetic factor or a closely linked gene. Some patients, blacks more than whites, do not have the marker at all. Perhaps the marker modifies immune responsiveness in the disease; or perhaps, it is a facilitator or receptor for a triggering agent. Various infectious causes--Shigella, Salmonella, Yersinia, Chlamydia--have long been suspected, but never established. Bacteria known to have the same amino acid sequence as certain body substances may be at the center of the disease process--perhaps initiating an immune response that continues as the resulting antibodies keep reacting against the similar and always present substance. A promising new model in which human genes are transplanted into mice has provided an opportunity to learn more about the relationship between bacteria and genes.

Scleroderma. Scleroderma is a serious disease that results from excessive production of collagen, the basic element of the body's connective tissue. Scleroderma means "hard skin," and this is one of its most striking symptoms. The disease may also affect small blood vessels and various internal organs. The cause of the disease is unknown. Dominant hypotheses concerning the etiology of scleroderma center around immunologic, connective tissue, and vascular abnormalities. The current level of support for research in this area is modest. Additional research is needed on the abnormalities of vasoregulation responsible for the pathogenesis of Raynaud's phenomenon, an early sign of scleroderma; on the neurogenic control of the microcirculation; and on interactions between endothelial cells, fibroblasts, lymphocytes and smooth muscle cells. The availability of the tight skin mouse, an animal model that mimics features of scleroderma, should help to elucidate the events responsible for this disease.

The recent epidemic of the eosinophilia-myalgia syndrome associated with use of L-tryptophan represents an illness closely related to scleroderma. Other environmentally derived models of the disease have been previously reported. Further study of these diseases may offer clues to the pathogenesis of scleroderma. The NIAMS plans to encourage much needed research in this important disease.

Sjogren's syndrome. Sjogren's syndrome is an autoimmune disorder of unknown cause, characterized by dry mouth, dry eyes, and, often, the simultaneous occurrence of other rheumatic diseases, such as rheumatoid arthritis. Patients may have arthritis, muscle inflammation, nerve damage, kidney disease, and still other features.

Following a January 1989 conference on the diagnosis and treatment of Sjogren's syndrome, investigators met to identify needs and opportunities for research; including: standardization of diagnostic criteria, epidemiologic studies, and investigations into the possible role of viruses and genetic factors in the causation of the disease. An animal model for Sjogren's syndrome has been recently developed, and this may provides an opportunity to study autoimmune mechanisms as they relate to Sjogren's syndrome.

Acquired Immune Deficiency Syndrome. Many patients with HIV infection manifest one or more types of skin disease during their

illness. In some individuals, epidermal cells harbor the HIV agent, and these cells could play an important role in the spread of HIV to other tissues. Patients with AIDS also develop several different types of arthritis, and these are under investigation. Additional research is needed to better understand these phenomenon. Such study may yield valuable insights into both the nature of AIDS and the nature of the skin and rheumatic diseases related to AIDS.

Heritable disorders of connective tissue. These often devastating disorders include: osteogenesis imperfecta, which can cause easy fractures in children and infants, even before birth; Marfan syndrome, which afflicts the skeletal system, eyes, heart, blood vessels, and lungs; Ehlers-Danlos syndrome, in which fragile tissues can lead to blood vessel rupturing and frequent joint dislocations; the chondrodysplasias, which produce skeletal deformities and short stature; painful, life-threatening epidermolysis bullosa, among others. Our April 1990 workshop on these disorders will review and make recommendations on research needed to understand the genetically determined defects of the proteins or other chemicals that lead to fragility, excess elasticity or defective growth of the bone, cartilage or skin in these disorders. Additional funds would be needed to support these recommendations.

Osteoporosis. Osteoporosis is the leading cause of bone fractures in postmenopausal women and in elderly persons, and it afflicts as many as half of all women in the United States over 45 years of age. The direct and indirect costs of osteoporosis in this country are estimated at $10 billion annually. This year, the NIAMS cosponsored a major workshop on research in osteoporosis at which investigators from across the country gathered to report on the latest research findings. Following the conference, the session leaders assembled to assist the NIAMS in formulating research recommendations that will be included in a report being prepared at the request of the Congress.

The following were recommended for future emphasis: (1) the direct effects of estrogens and androgens on bone cells to understand the impact of sex steroid deficiency on bone remodeling; (2) studies on the 3-dimensional architecture of bone to better understand how this contributes to risk of fracture; (3) more studies on racial and ethnic groups with lower fracture incidence to identify possible protective factors; (4) important new developments in the biochemical assessment of bone loss could be fruitfully exploited to enable clinicians to predict the rate of bone loss in an individual; (5) investigations of the action of fluoride directly on bone cells to elucidate how the bone forming action of fluoride may be exploited to therapeutic advantage; (6) more investigation is needed in the therapeutic use of growth factors, especially, development of bone-specific analogs of hormones and growth factors.

NIAMS-sponsored clinical trials have raised important questions about the efficacy of sodium fluoride in the treatment of osteoporosis. This has highlighted the need for additional research on other promising therapeutic modalities. Recruitment of new investigators into this field is of major importance, and this would be enhanced by availability of more funds.

Osteoarthritis. This is the most common form of arthritis, and it is a leading cause of pain and disability. X-ray evidence of the disease can be found in one-third of adults and nine of ten women over age 75. Five years ago, an NIAMS-sponsored workshop made some 130 specific research recommendations in this field, identifying promising opportunities in the broad areas of: difference between types of OA; population differences (in China OA is endemic in a younger population); the role of trauma in disease development; cartilage changes related to disease; the role of underlying bone, ligaments and tendons in disease development; cartilage repair once the disease process has begun; and inflammation as a primary or secondary event. Opportunities for new advances are present in epidemiology, genetics, pathophysiology, and treatment.

Low-back pain. In 1988, the NIAMS and the American Academy of Orthopaedic Surgeons cosponsored a scientific workshop to assess recent progress in low-back pain research. The primary purpose of the workshop was to develop a detailed guideline of important opportunities for future research. Sixty-three research recommendations were put forward covering four anatomical areas: nerve; disc; muscle; and other support structures. Many of the studies suggested will require collaboration from experts in several scientific disciplines. Both clinical and basic science projects were suggested. A strong encouragement was presented for collaborative studies by experts in magnetic resonance and others studying low-back pain.

Paget's disease. Paget's disease is a severely deforming acquired disease of bone. While the prognosis for Paget's disease has improved over the past 10 years, the etiology remains a mystery. None of the current treatment regimens is ideal for all patients. The basic structure and cell functioning of pagetic bone needs more scientific study. The increased turnover rate of Paget's bone cells makes them a potentially good model system for studies on basic bone cell biology. A program announcement requesting research on etiology, genetics, bone cell biology, and clinical studies was issued in December 1988; and additional research could be encouraged with higher funding levels.

Muscle biology. Research in the Muscle Biology Program provides a foundation for understanding how muscle develops and functions normally and how it goes awry in disease, knowledge essential for many other research areas within the Institute's mission, including those of musculoskeletal fitness and sports medicine. NIAMS-supported research particularly focuses on structure-function relationships of how muscle force is generated and on the metabolism of muscles at work. The relationship of chemical structure of muscle protein to muscle function is poorly understood. In April 1990, the NIAMS sponsored a workshop on molecular genetics and genetic engineering in muscle to analyze in detail the state of knowledge of the structures and functions of the molecules that make up muscle, and to study and stimulate further research in this area.

Musculoskeletal fitness and sports medicine. A recent program announcement on musculoskeletal fitness and sports medicine has generated many applications in the areas of repair of injuries, soft

tissue inflammation related to injury, and biomechanics of falls and injuries, and there are many good applications pending in these areas. Also, the opportunity exists for much greater work in the epidemiology and prevention of sports injury and in treatment trials on different repair procedures.

Epidermolysis bullosa. This rare devastating illness causes blistering of the skin and linings of the mouth and gastrointestinal tract. In its worst forms the illness is lethal. A national registry, supported by the NIAMS, has been established. Researchers have identified specific anatomic layers in the skin that are subject to injury, and they are beginning to understand the mechanisms of injury. However, the primary causes of the illness and most effective treatments remain to be identified.

Keratins. Keratins are found in skin, hair and nails. Keratins make up ninety percent of the proteins of the outer layer of skin, which serves a barrier to the environment, protecting the body from loss of water and preventing penetration by toxic chemicals. There is considerable interest in the genes responsible for making keratins, which occur on different chromosomes. Abnormal control and regulation of the genes may be implicated in scaling diseases of the skin. A transgenic mouse model expressing abnormal keratin has been created. Much of this important work on keratin and other key skin proteins is being conducted by NIAMS' new Laboratory of Skin Biology.

Fundamental understanding of skin biology at the molecular and genetic levels is essential for the development of new strategies to treat skin diseases ranging from such disorders as psoriasis to rare keratinizing diseases such as the ichthyoses and epidermolytic hyperkeratosis.

Biology of hair. Hair undergoes a complicated biologic cycle that can be influenced by both extrinsic and intrinsic factors. Some loss of hair occurs daily and certain forms of hair loss, such as occurs in males, are extremely common. Others such as alopecia areata, in which patchy loss of hair can progress to total loss on the head or the entire body, are less common. Few clues exist as to why this disorder occurs. Recent improvements in culture techniques--particularly the development of organ culture that allows hair growth and the development of new animal systems to test certain therapies--at last provide the opportunity to understand and control this distressing problem. The NIAMS has convened an expert group to advise the Institute on directions for further research on alopecia.

Sunlight and skin. The NIAMS sponsored a successful Consensus Development Conference on the Effects of Ultraviolet Radiation on Skin, focusing on photoaging, and on effects of sunblockers and on changes in the ozone layer. The Conference made several recommendations for further research, including: (1) research to define the immunologic effects of UV radiation on the skin; (2) studies on the differences between sun-induced aging and chronologic aging; (3) development of a current database on the incidence of non-melanoma skin cancer; (4) further research to define the action spectrum of sunlight and UV radiation in the pathogenesis of melanoma; (5) further research on the biologic effects of UVA radiation in regard to its photoaging and immunologic effects; and

development of more effective sunscreens and the monitoring of the risk/benefit ratio of the widespread, long-term use of sunscreens.

Molecular biology of skin diseases. Many common skin diseases, among them atopic dermatitis, ichthyosis, epidermolysis bullosa, and psoriasis, have an inherited basis. The genetic basis of these illnesses is not understood. Recent advances in molecular biology make it possible to identify genes, and the associated abnormalities, that are related to these diseases, and further research would be of value.

Wound healing. How scar tissue forms, how to control formation of scar tissue and how to improve defective wound healing are critical questions. Answers to these questions would provide basic information about skin biology that would have wide implications in other fields. The NIAMS wishes to advance research in this field.

DOWNWARD NEGOTIATIONS

Mr. Early. Will there be downward negotiations in competing and non-competing grants under the budget request? How big of a cut are you taking this year?

Dr. Shulman. Yes, the downward negotiations in new and competing research is projected to be 11.5 percent under the President's FY 1991 budget request. Noncompeting research project grants will be reduced 12.0 percent from recommended levels.

Mr. Early. Dr. Shulman, the NIAMS has faced signficiant downward negotiations since the institute was created. What effect will these reductions have on the research programs supported by the Institute?

Dr. Shulman. Comments from investigators indicate that when grants are reduced, technicians and collaborators are removed from projects because the largest portion of grant funds support salaries. In addition, subprojects of funded applications may have to be deleted. The effects, therefore, are to slow progress, and in some cases, to leave major areas of planned research unexplored.

Mr. Early. What effect has this had on the NIAMS ability to mount and sustain a vigorous and broad-based extramural program?

Dr. Shulman. The total number of grants the NIAMS can pay is protected, in part, by effecting downward negotiations in funded grants. To protect individual grantees as much as possible, the NIAMS has had to restrict funding for centers, other research and R&D contracts. These mechanisms have been kept level.

Individual grantees often need to reduce staff or postpone projects or purchase of equipment because of such reductions. These postponements, in turn, slow the pace of the research. When funding becomes unduly uncertain, new investigators do not enter the field, and senior investigators leave research. The cumulative effect is the slowing of research progress and the discouragement of researchers.

Mr. Early. I see from your budget justification that you will fund the same number of research centers (26) in FY 1991 as in FY 1990. However, you plan to do so with less money than you allocated in FY 1989. What is the amount of downward negotiations in research centers?

Dr. Shulman. The negotiated reductions for FY 1991 for research centers is projected to be 17.0 percent. This compares with 15.0 for FY 1990 and 14.0 percent for FY 1989.

Mr. Early. What effect is another year of substantial downward negotiation having in these centers and their research programs?

Dr. Shulman. Centers grants are funded for 5 years; therefore, one advantage of center funding is the stable level of support to pursue the work. However, double-digit downward negotiations, now in their third year, nullify this advantage by putting a real strain on these labor-intensive grants. Center grants, even more than regular research grants, largely fund personnel because the emphasis is on working up new research leads and also on providing much needed technical research support in the core units. In some cases personnel has been reduced or supply budgets. In at least three instances, patient studies have had to be downscaled because the funds were inadequate to continue as originally designed. Therefore, some of the important questions initially posed are not being addressed.

RESEARCH CENTERS

Mr. Early. What is the estimated full cost for research centers in FY 1991?

Dr. Shulman. The estimated full cost for research centers is $25.3 million, which is $4.3 million above the estimated request of $21.0 million.

Mr. Early. Provide for the record a list of current NIAMS Research Centers, and indicate the type of center, the associated cost, and whether it is up for renewal in either FY 1990 or FY 1991.

Dr. Shulman. The information follows.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

FY 1989 Funding for Centers

Multipurpose Arthritis and Musculoskeletal Diseases Centers

Boston University	Robert F. Meenan, M.D., M.P.H.	Boston, MA	$1,185,741
Brigham and Women's Hospital	Matthew H. Liang, M.D., M.P.H.	Boston, MA	982,488
Case Western Reserve	Roland W. Moskowitz, M.D.	Cleveland, OH	1,016,272
Hospital for Special Surgery	Charles L. Christian, M.D.	New York, NY	1,052,846
Indiana University	Kenneth D. Brandt, M.D.	Indianapolis, IN	923,225
Northwestern University	Frank R. Schmid, M.D.	Chicago, IL	1,179,619
Scripps Clinic & Research	Eng M. Tan, M.D.	La Jolla, CA	482,008
Stanford University	Halsted R. Holman, M.D.	Palo Alto, CA	855,085
Univ Alabama, Birmingham	William J. Koopman, M.D.	Birmingham, AL	859,653
Univ California, Los Angeles	Bevra H. Hahn, M.D.	Los Angeles, CA	914,690
Univ California, San Francisco	Ira M. Goldstein, M.D.	San Francisco, CA	817,596
Univ Connecticut Health Center	Naomi F. Rothfield, M.D.	Farmington, CT	1,169,043
Univ Michigan at Ann Arbor	William N. Kelley, M.D.	Ann Arbor, MI	1,202,804
Univ N Carolina, Chapel Hill	John B. Winfield, M.D.	Chapel Hill, NC	935,687
		Total:	13,576,757

NOTE: None are up for renewal in FY 1990.
Only Scripps Clinic & Research is up for renewal in FY 1991.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

FY 1989 Funding for Centers

Specialized Centers of Research

Creighton University	Robert R. Recker, M.D.	Omaha, NE	$838,789
Duke University	Barton F. Haynes, M.D.	Durham, NC	716,677
Helen Hayes Hospital	Robert Lindsay, M.D., Ph.D.	West Haverstraw, NY	719,639
Indiana Univ Sch of Medicine	Kenneth D. Brandt, M.D.	Indianapolis, IN	691,876
Rush Presbyterian-St. Luke's Med Center	Klaus E. Kuettner, Ph.D.	Chicago, IL	659,140
Univ Tennessee Center Health Sciences	Andrew H. Kang, M.D.	Memphis, TN	891,545
Univ Texas SW Med Center - Dallas	Peter E. Lipsky, M.D.	Dallas, TX	734,784
University of Minnesota	Roby C. Thompson, Jr. M.D.	St. Paul, MN	663,484
University of Pennsylvania	Carl T. Brighton, M.D.	Philadelphia, PA	834,255
		Total:	6,750,189

NOTE: None are up for renewal in FY 1990 or FY 1991.

Skin Diseases Research Centers

Case Western Reserve University	David R. Bickers, M.D.	Cleveland, OH	$317,532
New York University	Irwin M. Freedberg, M.D.	New York, NY	314,015
		Total:	631,547

NOTE: None are up for renewal in FY 1990 or FY 1991.

Grand Total: 20,958,493

CLINICAL TRIALS

Mr. Early. Is this substantial level of downward negotiation in RPG's and centers having any adverse effect on your ability to mount and conduct clinical trials?

Dr. Shulman. The NIAMS supports clinical trials through research contracts (NOIs), research project grants (ROIs), program project grants (POIs), research center grants (P60s & P50s), and the Institute's Intramural Program. The major extramural clinical trials have been conducted through a series of contracts with the Cooperative Systematic Studies of Rheumatic Diseases. These contracts are cost reimbursement contracts. All negotiations for the costs of these studies were completed prior to the award of the contracts.

The clinical trials that are being conducted through ROIs, POIs, P50s and P60s have had the downward negotiation rates applied to their grants. The principal investigators of each study have the responsibility for making appropriate adjustments in their research plans to accomplish the completion of the clinical trials as proposed in their grant applications. The adverse effects of downward negotiations on grant-supported clinical trials should be similar to the effects on other grant-research projects. It is likely that with reduced levels of funding the trials will not be done as expeditiously or completely as proposed in the original applications, but these effects would not be specific to clinical trials.

Mr. Early. Doctor, will you have to curtail any ongoing clinical trials under your FY 1991 budget request? Are you having to "stretch things out"?

Dr. Shulman. The NIAMS has a relatively small clinical trials program, amounting to less than 4 percent of the total budget. The FY 1991 request will allow us to continue ongoing clinical trials at their currently planned levels, as long as no new trials are started.

However, because the NIAMS clinical trials program has remained small, it has been necessary to stretch out the planning horizon for some of the studies, and to conduct them over a greater number of years than would be otherwise necessary. The overall result is a reduction of available research data and a consequent delay in obtaining definitive answers regarding the efficacy and safety of therapeutic interventions that are under study. The NIAMS is not planning to terminate or curtail any ongoing clinical trials.

Mr. Early. Are there any high priority clinical trials which are ready but cannot be initiated because of lack of funds in the FY 1991 Request? If so, please provide a list of these, along with a brief description and the associated costs, including first year costs.

Dr. Shulman. Yes. The following is a list of clinical trials that could be started in FY 1991 with additional funding and personnel.

Cooperative Agreements:

Treatment of the Late Stages of Lyme Disease:

Questions remain about the best treatment(s) for the late manifestations of Lyme disease, such as chronic erosive arthritis and various neurologic complications. Drawing upon experience with treatments devised for the later stages of syphilis (a spirochetal disease with which Lyme disease shares many features), this clinical trial would be a double blind, placebo controlled clinical trial of high doses of intramuscular aqueous procaine penicillin G with probenecid daily for 10 days followed by weekly doses for three additional doses. An alternative regimen could be daily high doses of intravenous aqueous penicillin G for 10 days following by three weekly intramuscular injections of benzathine penicillin G. For patients with penicillin allergy, the current recommended treatment for late syphilis is two grams of tetracycline daily for 30 days. Perhaps this would work for Lyme disease, as well. This could be a relatively small clinical trial in terms of sample size and be of short duration.

	FY91	Total Project Costs	Duration
Coop. Agreements	$500,000	$1,100,000	2 years

Treatment of Erythema Migrans:

The early treatment of erythema migrans should prevent the development of the later stages of Lyme Disease. The use of oral penicillins, erythromycin, and/or tetracycline could be evaluated with a double blind placebo controlled crossover trial(s). Given the non-uniformity of progression of erythema migrans to Lyme arthritis and other later manifestations of Lyme disease, this study(ies) would need relatively large sample sizes (probably on the order of 100 to 200 per comparison) to assure sufficient power for detection of any benefit. Therefore, multiple centers would probably be needed. The duration of treatment needed to prevent progress from erythema migrans to later Lyme disease is unknown; therefore, various durations of treatment would be tested.

	FY91	Total Project Costs	Duration
Coop. Agreements	$1,000,000	$2,100,000	2 years

Safety and Efficacy of Human Calcitonin in the Treatment of Osteoporosis

Calcitonin is one of the few agents that has been reported to have the capacity of forming new bone. A new form of human calcitonin has recently been developed which should cause less sensitivity reactions than the salmon calcitonin currently in use. Also a new nasal spray delivery format may be more acceptable than the present injection methods. Four clinical centers are envisioned for a two year study.

	FY91	Total Project Costs	Duration
Coop. Agreements	$1,000,000	$2,280,000	2 years

Safety and Efficacy of Bisphosphonates in the Treatment of Osteoporosis

Bisphosphonates (or diphosphonates) inhibit bone resorption by inhibiting hydroxylapatite crystal dissolution and inhibit the activity of osteoclasts. One treatment with bisphosphonates appears to form a relatively permanent blockade against bone remodeling. These compounds have been studied for the treatment of tumor-associated hypercalcemia and Paget's disease of bone, but its use in the treatment of osteoporosis needs to be studied in a well-designed controlled clinical trial. Four clinical centers are envisioned for a two year study.

	FY91	Total Project Costs	Duration
Coop. Agreements	$1,000,000	$2,280,000	2 years

Early and Aggressive Combination Therapies for Rheumatoid Arthritis

There is growing conviction on the part of many rheumatologists that early and aggressive use of combinations of disease modifying drugs should be evaluated for treatment of rheumatoid arthritis. The rational for combining drugs is to exploit the different modes of action of different drugs, hopefully improving efficacy (perhaps through synergism), and allow one to use lower doses, hopefully lowering toxicities. One such combination is currently under study through the CSSRD: the combination of methotrexate and auranofin. An systematic approach to the testing of the large number of possible combinations could be mounted and modeled after the very successful cancer therapy evaluations (MOPP, BOPP and all the rest.) These evaluations established a very productive network of clinical centers across the United States that have cooperated in the testing of numerous anti-cancer therapies. A series of simultaneous and evolving protocols of combination therapies for rheumatoid arthritis are envisioned. Pilot and feasibility studies would be an important component of the program. Long term follow-up (at least five years) would be needed to access the impact of these protocols as compared to current practice.

	FY91	Total Project Costs	Duration
Coop. Agreements	$600,000	$9,000,000	5 years

Contracts:

Safety and Efficacy of 4-hydroxyphenylretinamide in Patients with Rheumatoid Arthritis.

Seven clinical centers supported through contracts with the NIAMS and with support and cooperation of McNeil Pharmaceutical (the drug's manufacturer) would be needed for this double-blind, placebo-controlled clinical trial of 4-hydroxyphenylretinamide therapy for rheumatoid arthritis.

	FY91	Total Project Costs	Duration
Contracts	$1,500,000	$5,400,000	3 years

Epidermal Growth Factor in the Treatment of Epidermolysis Bullosa.

A placebo controlled clinical trial of epidermal growth factor would test the safety and efficacy of this promising new treatment for epidermolysis bullosa. A one time application appears to induce healing of the lesions seen in this disease. Patients identified through the Epidermolysis Bullosa Registry could be entered into the trial. Since the patients have multiple lesions, they could serve as their own controls with random assignment of treatment by lesion, not by patient.

	FY91	Total Project Costs	Duration
Contracts	$200,000	$600,000	3 years

Efficacy of 13-cis Retinoic Acid and Other Retinoid Derivatives in the Treatment of Keratinizing Disorders.

Retinoids are a highly promising group of therapeutic agents for a variety of dermatologic and rheumatic conditions. They appear to suppress cholesterol synthesis and have anti-inflammatory effects, which may explain their apparent efficacy in treating keratinizing disorders of the skin. A formal clinical trial of these agents would be undertaken.

	FY91	Total Project Costs	Duration
Contract	$1,000,000	$3,000,000	3 years

Use of Retinoids in the Treatment of Psoriatic Arthritis

Retinoids are a highly promising group of therapeutic agents for a variety of dermatologic and rheumatic conditions. The anti-inflammatory effects of retinoids on mononuclear and polymorphonuclear leukocytes may prove useful in treating psoriatic arthritis.

	FY91	Total Project Costs	Duration
Contract	$500,000	$1,025,000	2 years

Mr. Early. Will you be able to start any new clinical trials in FY 1991?

Dr. Shulman. The clinical trial to assess the efficacy of minocycline in the treatment of rheumatoid arthritis is expected to get started in late 1990 and will represent a major effort for the Institute during 1991, too. Also, many of the clinical trials that the Institute supports are researcher-initiated projects. What these are depend upon the applications we receive and how they fare during peer review. The NIAMS has actively solicited clinical studies of therapeutic and preventive interventions for Lyme disease through a Program Announcement. We anticipate that we will continue to receive applications responsive to that announcement.

Mr. Early. What is the primary method at the NIAMS of supporting clinical research?

Dr. Shulman. The primary method the NIAMS has used to support clinical research is the research project grant mechanism. To a lesser degree, the Institute supports clinical research through research centers, research contracts, and the Intramural Program.

Mr. Early. Is patient accrual for clinical trials a problem in your Institute? If so, what steps could be taken to improve the situation?

Dr. Shulman. Recruitment of sufficient patient volunteers for clinical trials is often a problem for the investigators, but this has not been a major problem for studies supported by the NIAMS. One exception, is a clinical trial of hydroxychloroquine (an anti-malarial agent that has been used to treat rheumatic conditions) in the treatment of early systemic lupus erythematosus. This study is being conducted by the centers participating in the Cooperative Systematic Studies of Rheumatic Diseases.

RESEARCH CAREERS

Mr. Early. Doctor, how would you assess the adequacy of research manpower in the fields of concern to your institute?

Dr. Shulman. A constant influx of well-trained and enthusiastic investigators is essential for accomplishment of the missions of the Institute. The missions include many medical and scientific disciplines, so one must assess adequacy both in terms of numbers and program distribution. The total influx seems level, as measured by the number of research grant applications, but this is insufficient for successful follow through of research opportunities. There are shortages of new researchers in several critical areas, such as orthopedics, or molecular genetics and structure, which are of major importance to understanding the maintenance of healthy skin, muscle, bone and connective tissue. This weakness is also present in the distribution of applications for individual fellowships and research career awards, which causes concern for future adequacy of the pool of new investigators.

Mr. Early. Would you summarize for us the types of research career programs the NIAMS supports?

Dr. Shulman. The NIAMS supports research career development through two major mechanisms. The first mechanism includes research training through individual fellowship awards and institutional training grants, authorized under NRSA. These awards support directed training of individuals in research methodologies in an active research setting. In the NIAMS, the fellowships largely support people who have recently acquired a doctoral degree and plan on conducting research of interest to the Institute. The second class of programs includes several types of awards which facilitate development into independent researchers, who can design and conduct well focussed investigations. This includes the Clinical Investigator Award, which provides further support for clinicians with prior research training so that they can consolidate their prior training and research interests into an independent project. The successful candidate for this award usually has had prior support as a research fellow. The Physician Scientist Award is more appropriate

for clinicians who have had little formal research training. It is divided into two phases. The first is an intensive didactic period, usually two years, which includes course work and laboratory experience in basic science disciplines. The second phase provides for this knowledge to be applied to a clinical research problem, so that the recipient will be able to develop an independent research project. The NIAMS also provides Research Career Development Awards, which are usually made in conjunction with research grant support. These awards allow recipients to spend a greater proportion of their time on active research by providing relief from administrative and clinical duties. This award assists candidates in establishing themselves further as research leaders.

PREVENTION AND EDUCATION

Mr. Early. To what extent does your institute support prevention and education programs? What kind of activities are supported?

Dr. Shulman. A significant portion of the efforts of our Office of Prevention, Epidemiology and Clinical Applications, Office of Scientific and Health Communications, and the National Arthritis and Musculoskeletal and Skin Diseases Information Clearinghouse involve providing information about the prevention of diseases such as low back pain, osteoporosis, Lyme disease, and overexposure to ultraviolet light, as well as prevention of disability from other diseases such as arthritis and systemic lupus erythematosus.

Patient and public information programs have been expanded and improved. The National Arthritis and Musculoskeletal and Skin Diseases Clearinghouse has become a separate entity, and it provides a new focus for many of these efforts. We have developed special information packages in these and other areas for the public and bibliographies for several of these topics for health professionals.

Initiatives in osteoporosis include reprinting a booklet based on our my "Medicine for the Layman" presentation on osteoporosis, continuing to provide speakers and do radio and television interviews, and writing research news stories on major findings and the recent scientific workshop. We would like to mount additional efforts in this area including collaborating with the National Osteoporosis Foundation and the Arthritis Foundation to plan, develop, and promote preventive interventions for osteoporosis and working with the local and national food industry to reach consumers with information about recommended levels of calcium intake and, in particular, the bioavailable sources of calcium for the prevention of osteoporosis.

In osteoporosis, emphasis is being placed on prevention and on the identification of persons at high risk. Active young women have been recently shown to have a higher bone mass than sedentary women. Weight-bearing exercise is necessary for bone health. Activities in which the muscles work against gravity, such as walking or jogging, may help to reduce bone loss. Furthermore, a well-maintained musculoskeletal system may be important in both avoiding falls and making protective responses, should a fall occur.

It is now clear that estrogen replacement therapy, begun at menopause, can significantly reduce the number of fractures caused by osteoporosis. Studies are under way to determine the best combination of estrogen and progesterone in the prevention of osteoporosis. Differences between groups may indicate genetic or environmental risk factors and suggest new approaches to prevention. The ongoing Third National Health and Nutrition Examination Survey conducted by the National Center for Health Statistics is studying in detail issues concerning the prevalence and risk factors in osteoporosis.

In the area of Lyme disease, we have several ongoing efforts and projects. Last May, we brought Dr. Anita Curran from the Robert Wood Johnson School of Medicine in New Jersey (formerly Commissioner of Health of Westchester County, New York) to the NIH campus to lead an NIH Prevention Seminar on preventing Lyme disease. Institute staff participated at the Congressional briefing and press conference in anticipation of Lyme Disease Awareness Week last July. We are collaborating with the National Institute of Allergy and Infectious Diseases (NIAID) and the Centers for Disease Control on a brochure on Lyme disease for the public and with NIAID on a poster/ diagnostic wall chart for physicians.

One of our goals is to improve the outcome of systemic lupus erythematosus in high risk populations and prevent complications and premature death and disability. The prevalence of lupus among black females is about nine times that observed in white females. There are also indications that black females do not have as ready access to health care as white females. They may not be getting available treatments for lupus early in their disease, resulting in a greater frequency of complications than necessary. A task group on Lupus in Minority Populations has been meeting on a regular basis to develop new educational materials for patients and health professionals. We are developing materials for community organizations that reach black women age 12-44 and a slide/narrative program for health professional groups that address these issues.

RHEUMATOID ARTHRITIS

Mr. Early. Doctor, I've been told that we may be able to develop a vaccine for arthritis .. rheumatoid arthritis, I believe, within the decade. Is this correct? What can you tell us about this?

Dr. Shulman. An ideal treatment for autoimmune diseases and a useful approach for arthritis in humans would be a safe and nontoxic means of specifically neutralizing the autoreactive lymphocytes responsible for the disease. This goal has been realized in experimental autoimmune animal models by immunizing rats or mice against their own autoimmune cells such that the animals generate an immune response specifically repressive to the disease-producing lymphocytes. This maneuver, termed lymphocyte vaccination, was demonstrated to be effective against adjuvant arthritis using some, but not all, autoimmune helper T-lymphocyte lines.

It has been reported that T-lymphocytes, otherwise incapable of triggering an immune response, can be transformed into effective

immunogens by treating the cells in vitro with hydrostatic pressure. Inoculating rats with pressure-treated cells induced early remission of established adjuvant arthritis as well as resistance to subsequent disease.

These results have demonstrated that effector T-lymphocytes suitably treated may serve as agents for specifically controlling the immune system. It appears that autoimmune T-lymphocytes can be used as specific therapeutic (suppressive) agents in experimental autoimmunity. The possible application of T-lymphocyte vaccination to clinical (human) autoimmune diseases remains to be explored.

LASER RESEARCH

Mr. Early. Does the NIAMS support research on laser treatment?

Dr. Shulman. The NIAMS has supported laser research as it relates to skin disease through both the regular research grant mechanism and through the Small Business Innovative Research grant mechanism. Basic studies of laser tissue interaction particularly in the skin have been supported through the regular research grant mechanism primarily at Harvard and Massachusetts General Hospital for almost ten years. Dr. John Parrish, Principal Investigator of these research project grants and Chairman of the Department of Dermatology at Harvard received the Marion B. Sulzburger Memorial Award and Lectership of the American Academy of Dermatology in 1988 for these pioneering research efforts. Through the Small Business Innovative Research Grant mechanism the NIAMS has supported the development of the laser that is now commercially available and has become first choice treatment of Portwine stain in the skin. The NIAMS is also supporting research into the use of lasers for the treatment of pigmented lesions of the skin and in the musculoskeletal program, the development of lasers for the percutaneous treatment of spinal disc disease; both of these also through the Small Business Innovative Research Program.

The basic understandings of laser tissue interactions hold the promise for the development of treatments for multiple different diseases not only those within the purview of the NIAMS. Many of these treatment modalities will depend upon the interaction of high intensity laser light of appropriately selected wavelength with chemicals that have been selectively introduced into certain diseased or abnormal tissue. These potential applications are in the areas of atherosclerosis and tumor ablation, among others. The combined support of basic laser tissue interaction research through the regular research grant mechanism and the more targeted disease oriented treatment development primarily through the Small Business Innovative Research grant mechanism appears to have been a very productive combination, in translating basic science to clinical medicine, and will continue to receive support by this Institute.

Mr. Early. What accomplishments can you report from the SCOR centers?

Dr. Shulman. The research results beginning to come from the SCOR centers are truly exciting. These can be presented in three areas: rheumatoid arthritis, osteoarthritis, and osteoporosis.

Rheumatoid Arthritis. Researchers at Duke University are examining the immunologic changes seen in inflamed joints of rheumatoid arthritis (RA). One study is focused on the interaction between T cells and nonlymphoid cells rheumatoid joints and the molecular mechanisms through which inflammation occurs. Other investigations concern regulation of inflammatory mediators. A related study deals with patients to determine and improve their pain coping skills.

At the University of Tennessee, Memphis, the focus of several research projects is on regulation of destructive mediators in RA. The investigators are examining the molecular characteristics of cartilage that trigger immune reactions and the activation of collagen-degrading enzymes.

The genetic and immunologic basis of RA is being investigated by the researchers at the University of Texas Southwestern Medical Center, Dallas. The genetic basis of rheumatoid factor an abnormal antibody) and immunoglobulin production in patients with RA are under study. The immunologic responses in RA are also being investigated with a special emphasis on categorizing patient response to therapy. Preliminary data suggest that a subset of patients with RA respond to therapy with non-steroidal antiinflammatory drugs in a fashion previously associated only with the more aggressive disease modifying drugs.

Osteoarthritis. At Rush-Presbyterian-St. Luke's Medical Center in Chicago, researchers are focusing on the biochemistry of the chondrocytes, the key cell type in making and maintaining cartilage. Using sub-populations of these cells, alterations by physical load and degradative enzymes are being investigated. Investigators are finding new characteristics of these special cells. The chondrocytes taken from superficial layers of cartilage are more prone to degrade matrix material than those taken from cartilage near the bone. Isolated chondrocytes also change their metabolism in response to mild electric current. The work being carried out will enable the investigators to better understand the stress experienced by the cells *in situ* when a load is put on the cartilage.

At Indiana University School of Medicine, the research focus is on osteoarthritis, particularly in the knee, as a failure of the joint as an organ: joint cartilage, subchondral bone, synovium, ligaments, cartilage and the neuromuscular apparatus. An experimental model of osteoarthritis is used. One important finding for human knee surgery to emerge from this experimental model is that if the nerves to the knee are left intact during knee surgery and care is taken to minimize bleeding, only a mild, non-progressive osteoarthritis develops. Other studies are analyzing aspects of the biochemistry of the whole tissue in experimental osteoarthritis to determine what tips the balance to overall degradation of cartilage.

One clinical study is examining the efficacy of analgesic doses of drugs rather than higher anti-inflammatory doses of these drugs in treating osteoarthritis of the hip and knee in patients. Early results suggest that the low analgesic dose is beneficial, but high doses may actually increase disability from osteoarthritis. These studies have important ramifications, since these drugs are readily available over-the-counter. With the potential for negative results from the efficacy of anti-inflammatory doses, drug companies would not undertake these studies.

The group at the University of Minnesota is concentrating on studying the response of the joint to damage. Repair or remodeling and the new functional state achieved depends upon joint loads, the nature of initial damage, the healing potential and the strength and healing of the remaining tissues. A model of knee damage has demonstrated that specific patterns of cartilage damage are seen that may explain how cartilage damage is propagated. Another study is aimed at determining how the loss of spinal discs translates into damage of the facets, the bony part of the spine. The knee motion of patients recovering from knee injury is another important area being studied by sophisticated methods.

Osteoporosis. At Creighton University in Omaha investigators are examining the etiology, prevention, and treatment of osteoporosis through several clinical studies. These include an examination of familial factors that might determine bone mass, bone loss through menopause, and other factors such as nutrition, physical activity and drug therapy that may be modified to increase bone mass.

Researchers at the University of Pennsylvania are studying the interrelationships of hormones, such as calcitonin and estrogen, and environmental stress, both mechanical and electrical, in the loss, inhibition and restoration of bone mass. Of special interest is the research showing that mechanical stress may be mimicked by electrical fields in promoting bone density. This research may lead to novel approaches in preventing osteoporosis.

The Helen Hayes Hospital is the site of research directed at the osteoclast as the key to understanding hormonal regulation of bone metabolism. Estrogen, vitamin D, and phosphate are also being investigated in clinical and animal studies for their role in osteoporosis as a disorder of bone remodeling.

Mr. Early. Do these centers (SCORs) focus on basic research, clinical research, or is it a mix?

Dr. Shulman. SCORs are required to include a mix of both basic and clinical research.

Mr. Early. What specific research topics are being concentrated on (in the SCORs)?

Dr. Shulman. There are three SCORs targeted to rheumatoid arthritis, three to osteoarthritis and three to osteoporosis.

Mr. Early. To what extent are the centers (SCORs) involved in clinical trials?

Dr. Shulman.

Osteoarthritis: One clinical trial -- analgesic vs antiinflammatory drugs in the treatment of osteoarthritis. (Brandt, Indiana).

Osteoporosis: Treatment strategies for OP (Lindsay, Helen Hayes) -- effect of strength training on bone density (Gallagher, Creighton).

Rheumatoid Arthritis: None.

MUSCULOSKELETAL FITNESS

Mr. Early. Briefly summarize your plans for research on musculoskeletal fitness and sports medicine in FY 1990 and FY 1991.

Dr. Shulman. The Program Announcement on Musculoskeletal Fitness and Sports Medicine has been highly successful in generating applications and obtaining new funding related to this field. Since many of these projects are new it will take some time until specific advances are forthcoming in both basic and clinical projects. A book on inflammation and healing from sports injuries is due to be published in the Summer 1990. This book resulted from a workshop held in 1989. Initiatives based on these findings will be announced late in FY 1990 or early in FY 1991.

YOUNG PEOPLE

Mr. Early. To what extent are your research activities focused on young people as opposed to adults?

Dr. Shulman. There is no special focus on young or adult people. Research is encouraged to understand activity and prevent and treat sports injuries in all age groups and at all levels of performance.

SPORTS MEDICINE

Mr. Early. Have you established a mechanisms to monitor the causes of athletic injuries and to identify ways of preventing them on scholastic athletic fields as required by your authorization?

Dr. Shulman. Little is clearly known about the risk of injuries facing students who participate in athletic activities. Adolescence, in particular, is the highest risk period for sports and recreational injuries. Approximately one in ten adolescent children per year receive hospital care for a sports and recreational activities injuries. Reports suggest that a variety of musculoskeletal conditions may result from the various sports that are frequently pursued at academic institutions. Although a number of data collection instruments have been developed to record different physical activity and injuries. little work has been done to test their validity or reliability. Uniform, valid and reliable data are needed to conduct population-based studies.

The NIAMS will conduct a workshop in 1990 on methods for monitoring the causes of athletic injuries to (1) review the current state of knowledge on data collection and analysis for student injuries associated with athletic activities and to (2) identify specific methods and mechanisms for developing a system to monitor these injuries in schools. Based upon information and advice gained at the workshop, NIAMS will implement a program for monitoring athletic injuries.

Many studies on sports injury (or sports traumatology) have been reported in the literature. Some common problems of uniformity in study design limit the comparability of results. A few of these issues are (1) definition of injury is not precise; (2) population-at-risk is not predetermined and (3) exact method of patient selection/exclusion is not stated. The planned workshop will address these concerns and give proper guidance for future research.

Epidemiologic research based on registry data is one way to describe the frequency of scholastic injuries and identify risk factors for their occurrence. Findings from these descriptive and analytic studies could be used to design effective and appropriate preventive strategies. Registry data could also be used to monitor changes over time and to target continued efforts toward reducing injury inducing activities in populations at greatest risk.

In April 1987, a program announcement on Musculoskeletal Fitness and Sports Medicine was released by the NIAMS to stimulate increased research efforts in exercise pathophysiology musculoskeletal fitness, and sports medicine. Well-designed approaches to injury data collection would enhance this newly stimulated research.

Public Law 99-158 specifically calls for "the establishment of mechanisms to monitor the causes of athletic injuries and identify ways of preventing injuries on athletic fields." Plans for this effort were also stimulated by staff discussions with leaders of the sports medicine field. For the past several years the Research Committee of the American Orthopaedic Society for Sports Medicine (AOSSM) worked on the development of a document that critiqued the current status of sports injury research, pointed to research opportunities, and provided some guidelines for further research activities. This resource, and the expertise of the individuals who prepared it will provide a foundation for further epidemiologic research development in the monitoring of athletic injuries.

DEVICES

Mr. Early. What progress can you report in research on devices that could substitute for damaged bone, muscle, and joints?

Dr. Shulman. Research is progressing on artificial and biological repairs to bones and joints. Many metallic implants now utilize porous surfaces to allow bone ingrowth and the potential for a more permanent attachment. Various coatings have been used to help enhance the bone growth. The long term success of this ingrowth technology is not yet proven. Recently a new coating technology was applied to the smooth surface of the total hip stem that inserts into the plastic pelvic cup. This material process leads to greatly reduced function and wear. In terms of biological replacements, enhanced compatibility matching, immune suppression and graft preservation technology have all allowed improved success of allografts for large bone segment or joint repairs. Research in muscle transplantation is in the early stages of development.

EPIDERMOYSIS BULLOSA

Mr. Early. What are the institute's plans in FY90 and FY91 in the area of epidermolysis bullosa research?

Dr. Shulman. The NIAMS plans to continue to support, both through the research grant and career mechanisms, basic research in the biology of the basement membrane zone of skin as it relates to the normal structure and function of skin and the abnormalities in Epidermolysis Bullosa. In addition, the NIAMS also supports the National Epidermolysis Bullosa Registry, consisting of four clinical sites and a coordinating center. In addition, NIAMS is supporting two workshops, one on Heritable Connective Tissue Diseases, and the other on the application of Linkage Analysis to Heritable Skin Diseases, both of which will include major sections on Epidermolysis Bullosa. Both workshops will provide information to the Institute to help direct future research efforts.

Mr. Early. Have there been any new findings or advances since last year that you can report on?

Dr. Shulman. There are new research findings concerning Epidermolysis Bullosa (EB). The first, and possibly very significant, is the discovery of an animal model for the recessive dystrophic form of Epidermolysis Bullosa. This model consists of inbred white alpine sheep discovered in Switzerland; they seem to develop an exact duplicate of the human disease. Ultrastructural examination of the animal's skin seems to show the absence of anchoring fibrils and type VII collagen as in human EB.

Further research concerns mechanisms of attachment of the epidermis to the dermis through the basement membrane zone, which is defective in EB. Advances include the determination that the anchoring fibrils, which consist of type VII collagen and which are

defective in the dystrophic forms of EB, can be elaborated by the epidermal cells above the basement membrane. This has implications for treatment using techniques such as cultured epidermal sheets.

Acquired EB, a type of EB in which antibodies are produced to type VII collagen, has provided these antibodies for use in determining exactly how anchoring fibrils function in attaching the epidermis to the dermis. They have been used to show that the end of the type VII collagen, which is not readily visible via electron microscopic examination, is found in the lamina densa of the basement membrane zone, whereas the visible banded portion of the type VII collagen is in the upper part of the dermis below the basement membrane itself. This investigation helps us to understand how molecules work to attach the epidermis to the dermis.

The Epidermolysis Bullosa Registry is collecting patients for specific epidemiologic and molecular genetic research projects. In one study, recessive dystrophic EB patients were genotyped. These patients demonstrated a higher than expected association with certain HLA markers. This may eventually aid in the localization and later isolation of the gene causing the disease. In another study, the Dowling-Meara form of EB seems to be in high enough prevalence within the registry data to make a reverse genetic linkage analysis feasible to search for the gene. The registry material is being analyzed to determine whether a full-blown genetic linkage analysis is reasonable at this time. In addition, the availability of patients through the registry should facilitate a much more efficient mounting of clinical trials when appropriate promising agents become available in the future.

Mr. Early. How much has been allocated for EB research in FY 1990 and FY 1991?

Dr. Shulman. In fiscal year 1989, the last year for which complete data is available, NIAMS supported 28 projects related to Epidermolysis Bullosa with total award of $5.4 million of which $3.9 million was directly related to the disease Epidermolysis Bullosa. It is expected that on the basis of scientific progress and new and continuing research grant applications that a similar or increased allocation of funds based on scientific competition will take place in Fiscal Year 1990 and in Fiscal Year 1991. Depending upon the response to the program announcement following the two workshops referred to above, the increase in Epidermolysis Bullosa related research may be expected to significantly exceed the rate of inflation.

PRIORITIES

Mr. Early. If an increase over your FY 1991 budget request is provided, how would you use these additional funds?

Dr. Shulman. With the appropriate funding, the NIAMS could fund 63 more research project grants, which would permit a payline at the 21st percentile, and this would provide funding for high quality research proposals in our various fields. Also a high priority are 4 more core research centers on skin diseases, 30 more research career grants, and 60 more research training positions. An increase

of 10 research contracts is a high priority so that the NIAMS can begin urgently needed clinical trials. The first priority for the Intramural Research Program is to add a Laboratory of Connective Tissue Research to complement our small orthopaedics program.

INITIATIVES LOST

Mr. Early. Will any significant new research initiatives or opportunities be lost or delayed by lack of funds in the FY 1991 budget request? Provide a list of these for the record, along with a brief description and the funding requirement associated with each.

Dr. Shulman. The Institute currently has unfunded applications in the full range of its categorical responsibilities. Some of the research needs and opportunities for the future, which could be undertaken with additional funds are listed below. The funding requirements associated with each are not shown, as these would depend on the funding payline. The NIAMS makes awards based on the number and quality of applications that are approved throught the peer review system.

Lyme disease. Additional research is needed to discover the mechanisms by which the infectious agent produces damage to different parts of the body. Although the disease responds well when treated early, diagnosis and treatment are complicated. The symptoms vary widely between patients, antibody tests are unreliable, and the course of the disease is unpredictable. Better treatments are needed for late occurring chronic skin and joint disease, and neurologic and cardiac complications. Together with the NIAID, the NIAMS issued program announcements and a request for applications and a number of high quality applications are pending.

Systemic lupus erythematosus. Many key questions concerning lupus remain unanswered and could be addressed by additional research: Why is lupus more common in women than in men and more common in blacks than in whites? Why does lupus begin mostly in young people? Does it run in families; and if so, is it inherited? What are the basic immunologic defects in lupus, and how do these defects cause damage to the organs of the body? What are the initiating factors that trigger these immunologic defects? A more intensive research effort is needed to address and answer these important questions. Additional treatment trials are also needed.

Rheumatoid arthritis. Additional research is needed to unravel mechanisms involved in generation and maintenance of inflammatory processes within joints and to identify factors that predispose to development of the disease. A recent workshop brought together basic scientists studying chemical and cellular components of the immune system and clinical investigators studying the association of genetically determined cell markers and susceptibility to rheumatic diseases. This interaction stimulated the formulation of number of important research questions on rheumatoid arthritis. The effort to discover and apply effective therapies has been hampered by the limited number of clinical trials on rheumatoid arthritis. Additional resources could be used to expand support for clinical research.

Arthritis in children. The NIAMS currently supports research to define genetic markers and factors that trigger the onset of pediatric rheumatic diseases and to determine why differences exist between pediatric and adult rheumatic diseases. Maturation of immune responses is suspected to play a role in arthritis. Because children have not been exposed to as many external antigens as adults, the search for immunologic clues in arthritis should be more straightforward in children. The hormonal environment in children differs from that of adults, and it is important to study the influence of these differences on the expression of immunity and inflammation. Detailed studies of the influences of growth on the destructive aspects of inflammation may provide new approaches to modifying the inflammatory process.

Spondyloarthropathies. Research is needed to understand the striking association between these diseases and the specific genetic tissue type, HLA-B27, still largely a mystery some 15 years after its discovery. It is not clear whether this is the major genetic factor or a closely linked gene. Perhaps the marker modifies immune responsiveness in the disease; or perhaps, it is a facilitator or receptor for a triggering agent. Bacteria known to have the same amino acid sequence as certain body substances may be at the center of the disease process--perhaps initiating an immune response that continues as the resulting antibodies keep reacting against the similar and always present substance. A promising new model in which human genes are transplanted into mice has provided an opportunity to learn more about the relationship between bacteria and genes.

Scleroderma. Scleroderma is a serious disease that results from excessive production of collagen, the basic element of the body's connective tissue. The cause of the disease is unknown. Dominant hypotheses concerning the etiology of scleroderma center around immunologic, connective tissue, and vascular abnormalities. Additional research is needed on the abnormalities of vasoregulation responsible for the pathogenesis of Raynaud's phenomenon, an early sign of scleroderma; on the neurogenic control of the microcirculation; and on interactions between endothelial cells, fibroblasts, lymphocytes and smooth muscle cells. The availability of the tight skin mouse, an animal model that mimics features of scleroderma, should help to elucidate the events responsible for this disease.

The recent epidemic of the eosinophilia-myalgia syndrome associated with use of L-tryptophan represents an illness closely related to scleroderma. Other environmentally-derived models of the disease have been previously reported. Further study of these diseases may offer clues to the pathogenesis of scleroderma.

Sjogren's syndrome. Following a January 1989 conference on the diagnosis and treatment of Sjogren's syndrome, investigators met to identify needs and opportunities for research; including: standardization of diagnostic criteria, epidemiologic studies, and investigations into the possible role of viruses and genetic factors in the causation of the disease. An animal model for Sjogren's syndrome has been recently developed, and this may provides an opportunity to study autoimmune mechanisms as they relate to Sjogren's syndrome.

Acquired Immune Deficiency Syndrome. Many patients with HIV infection manifest one or more types of skin disease during their illness. Patients with AIDS also develop several different types of arthritis, and these are under investigation. Additional research is needed to better understand these phenomenon. Such study may yield valuable insights into both the nature of AIDS and the nature of the skin and rheumatic diseases related to AIDS.

Heritable disorders of connective tissue. Our April 1990 workshop on these disorders will review and make recommendations on research needed to understand the genetically determined defects of the proteins or other chemicals that lead to fragility, excess elasticity or defective growth of the bone, cartilage or skin in these disorders. Additional funds would be needed to support these recommendations.

Osteoporosis. This year, the NIAMS co-sponsored a major workshop on research in osteoporosis at which investigators from across the country gathered to report on the latest research findings. Following the conference, the session leaders assembled to assist the NIAMS in formulating research recommendations. The following were recommended for future emphasis: (1) effects of estrogens and androgens on bone cells to understand the impact of sex steroid deficiency on bone remodeling; (2) studies on the 3-dimensional architecture of bone; (3) studies on racial and ethnic groups with lower fracture incidence to identify protective factors; (4) biochemical assessment of bone loss t enable clinicians to predict the rate of bone loss in an individual; (5) investigations of the action of fluoride directly on bone cells to elucidate how fluoride may be exploited to therapeutic advantage; (6) investigation in the therapeutic use of growth factors.

Osteoarthritis. Opportunities for new advances are present in epidemiology, genetics, pathophysiology, and treatment. Five years ago, an NIAMS-sponsored workshop made some 130 specific research recommendations in this field, identifying promising opportunities in the broad areas of: difference between types of OA; population differences; the role of trauma in disease development; cartilage changes related to disease; the role of underlying bone, ligaments and tendons in disease development; cartilage repair once the disease process has begun; and inflammation as a primary or secondary event.

Low-back pain. In 1988, the NIAMS and the American Academy of Orthopaedic Surgeons cosponsored a scientific workshop to assess recent progress in low-back pain research. The primary purpose of the workshop was to develop a detailed guideline of important opportunities for future research. Sixty-three research recommendations were put forward covering four anatomical areas: nerve; disc; muscle; and other support structures. A strong encouragement was presented for collaborative studies by experts in magnetic resonance and others studying low-back pain.

Paget's disease. The basic structure and cell functioning of pagetic bone needs more scientific study. The increased turnover rate of Paget's bone cells makes them a potentially good model system for studies on basic bone cell biology. A program announcement

requesting research on etiology, genetics, bone cell biology, and clinical studies was issued in December 1988; and additional research could be encouraged with higher funding levels.

Muscle biology. NIAMS-supported research particularly focuses on structure-function relationships of how muscle force is generated and on the metabolism of muscles at work. The relationship of chemical structure of muscle protein to muscle function is poorly understood. In April 1990, the NIAMS sponsored a workshop on molecular genetics and genetic engineering in muscle to analyze in detail the state of knowledge of the structures and functions of the molecules that make up muscle, and to study and stimulate further research in this area.

Musculoskeletal fitness and sports medicine. A recent program announcement on musculoskeletal fitness and sports medicine has generated many applications in the areas of repair of injuries, soft tissue inflammation related to injury, and biomechanics of falls and injuries, and there are many good applications pending in these areas. Also, the opportunity exists for much greater work in the epidemiology and prevention of sports injury and in treatment trials on different repair procedures.

Epidermolysis bullosa. A national Registry, supported by the NIAMS, has been established. Research has identified specific anatomic layers in the skin that are subject to injury and is beginning to understand the mechanism of injury. However, the primary causes of the illness, and potential treatments, remain to be identified.

Keratins. Abnormal control and regulation of the genes may be implicated in scaling diseases of the skin. A transgenic mouse model expressing abnormal keratin has been created. Much of this important work on keratin and other key skin proteins is being conducted by NIAMS' new Laboratory of Skin Biology. Fundamental understanding of skin biology at the molecular and genetic levels is essential for the development of new strategies to treat skin diseases ranging from such disorders as psoriasis to rare keratinizing diseases such as the ichthyoses and epidermolytic hyperkeratosis.

Biology of hair. Certain forms of hair loss, such as occurs in males, are extremely common. Others such as alopecia areata, in which patchy loss of hair can progress to total loss on the head or the entire body, are less common. Few clues exist as to why this disorder occurs. Recent improvements in culture techniques provide the opportunity to understand and control this distressing problem. The NIAMS has convened an expert group to advise the Institute on directions for further research on alopecia.

Sunlight and skin. The NIAMS sponsored a successful Consensus Development Conference on the Effects of Ultraviolet Radiation on Skin, focusing on photoaging, and on effects of sunblockers and on changes in the ozone layer. The Conference made several recommendations regarding sun exposure of Americans and for future research efforts.

Molecular biology of skin diseases. Many common skin diseases, among them atopic dermatitis, ichthyosis, epidermolysis bullosa, and psoriasis, have an inherited basis. The genetic basis of these illnesses is not understood. Recent advances in molecular biology make it possible to identify genes, and the associated abnormalities, that are related to these diseases, and further research would be of value.

Wound healing. How scar tissue forms, how to control formation of scar tissue and how to improve defective wound healing are critical questions. Answers to these questions would provide basic information about skin biology that would have wide implications in other fields. The NIAMS wishes to advance research in this field.

MAJOR REDUCTIONS IN SCOPE

Mr. Early. To what extent will there be major reductions in the scope of ongoing or new initiatives because of the FY 1990 funding level proposed?

Dr. Shulman. Overall, the NIAMS received a 4 percent increase in FY 1991 over the FY 1990 level for non-AIDS research. This will allow us to fund 150 competing research project grants. The payline for research project grants will be at the 14 percentile in FY 1991, the same as in FY 1989, but significantly below funding levels in previous years, and below the levels of most other Institutes at NIH. The award rate will increase only slightly from 18.5 percent in FY 1990 of 19.3 percent in FY 1991, well below prior award rates greater than 30 percent. Careers and other mechanisms will not increase in FY 1990, and Research Centers will be funded at a lower dollar level in FY 1990 than in FY 1989. The reductions in scope are major over the past 5 years, but not significantly different between FY 1990 and FY 1991.

RENAL FAILURE IN LUPUS

Mr. Early. Renal failure is one of the most feared complications of lupus. Is there any progress to report since last year?

Dr. Shulman. Twenty years ago, lupus patients had a very high mortality rate. Now with earlier diagnosis and more effective treatments most patients are living longer and leading more productive and often nearly normal lives. The fear of kidney disease (nephritis) is universal among patients with lupus. For severe lupus kidney disease, NIAMS intramural researchers are using chemotherapy drugs such as cyclophosphamide as a way of suppressing the immune system. They have demonstrated that high doses of the drug administered periodically (pulsed therapy) can reduce progression to kidney failure in patients with lupus nephritis. Capitalizing on the unique ability to follow patients on treatment protocols of very long duration, these scientists have defined a new treatment program for lupus nephritis that has markedly improved the outcome, but its effects were not visible until patients had been followed for 7 years and beyond.

Additional studies are underway evaluating other experimental therapies. Continued research on the immunologic features of SLE are expected to provide information to protect kidneys by prevention of immunologically mediated damage. Several investigators are examining the features of antibodies that specifically target kidneys, and other investigators are examining the cells in the kidneys that trap the antibodies. Sucess in either field will suggest new methods of treatment designed to prevent the occurrence of renal failure.

O'BRIEN KIDNEY CENTERS

Mr. Early. Is there any collaborative work going on with the O'Brien kidney centers (NIDDK)?

Dr. Shulman. There is no formal collaborative effort between the O'Brien Kidney Centers (NIDDK) and the NIAMS. Of the six (6) kidney centers, two (2) are focused on the relationship of kidney disease to hypertension and diabetes mellitus; two (2) study the relationship of urological obstruction to benign prostatic hyperplasia; and the last two contain individual projects associated with initial immune mediated glomerular injury and kidney dysfunction focused on cell damage and the mechanism of progressive glomerular sclerosis.

The NIAMS supports a number of projects which compliment some of the kidney center activities. These projects are concerned with the renal disease and tissue injury mechanisms associated with systemic lupus erythematosus. Additionally, there are projects which explore autoreactivity, immunoregulatory mechanism, immunoreactants and the role of immune complexes in SLE and other rheumatic diseases.

INTRAMURAL RESEARCH

Mr. Early. Doctor, NIAMS has established 2 new intramural labs --one in skin biology and one in orthopaedic research. What will these two labs add to your research program? What do you hope to accomplish?

Dr. Shulman. Two new laboratories have been created as recommended by an ad hoc advisory committee for development of the intramural program. First, a Laboratory of Skin Biology headed by Dr. Peter Steinert, an internationally renowned protein chemist and cell biologist, will serve as the focus for expanded research on normal and pathological processes in the development and function of the skin. Second, the Laboratory of Structural Biology Research, headed by an outstanding electronmicroscopist, Dr. Alasdair Steven, will deal with application and development of exciting new microscopy techniques for enhancing the images of molecules from muscle, skin, connective tissue and bone--molecules of particular relevance to the primary research mission of the NIAMS.

Mr. Early. How much is in your budget request for these two labs? Is this amount sufficient for mounting "solid" program? --For supporting these labs adequately in terms of personnel and equipment?

Dr. Shulman. The budget includes $1.1 million for these two laboratories. Some new space is expected to be available by the end of FY 1990, and this will be used to house a part of new laboratories. Additional new space has been promised for 1 year later, and this will permit completion of our plans for the Laboratory of Skin Biology. Once the laboratories are set up, additional scientists will be recruited to staff these new efforts. New funding will be needed to complete full staffing and expansion to the new space.

LYME DISEASE

Mr. Dwyer. New Jersey is also an endemic state for Lyme disease. Unfortunately, some physicians in my state believe that too little attention has been focused on improved testing as well as treating the chronic relapses which affect some Lyme disease sufferers. How much will NIAMS spend on Lyme disease in fiscal year 1990 and 1991?

Dr. Shulman. The NIAMS plans to spend $2.571 million on Lyme disease in FY 1990 and $2.703 million in FY 1991, an increase over the $788 thousand spent in FY 1989.

Mr. Dwyer. A recent breakthrough in Lyme disease diagnostics will lead to a higher number of reported cases. Unfortunately, the large number of false negatives from the old test has led some physicians to believe that "Lyme hysteria" was worse than the actual disease. What efforts will NIAMS take to make physicians aware of the new test and to encourage physicians to retest their patients?

Dr. Shulman. A new experimental test has been developed that has been very recently reported to be more sensitive than previous assays in detecting antibodies to fight the Lyme disease bacteria. These antibodies have been found to become trapped in "immune complexes," thereby escaping detection by conventional methods.

Researchers have reported that this test is more accurate than those previously employed, but a confirmation of these findings is needed before the practicality of the test can be firmly established. When that is achieved, efforts will be made to educate the medical community and have patients retested.

Mr. Dwyer. What research efforts are underway to study those Lyme disease patients who do not respond to short-term treatments with antibiotics?

Dr. Shulman. The NIAMS has paid special attention to funding research in evaluation and management of the chronic forms of Lyme disease. For example, it has been reported in a recent study that Lyme disease bacteria can be cultured from the blood of patients who have been treated for short periods of time with antibiotics. This is significant because it has been shown that nerve palsy may be related to active infection with live bacteria. It also indicates that not all antibiotics are equally effective against the bacteria, and that treatment may have to be continued for longer periods of time.

Vaccines to protect humans and domestic animals are under development. Research in an animal model has shown that certain immunization techniques are effective under some circumstances. Development of an effective vaccine in humans is expected to take some years.

Mr. Dwyer. What is in store for those individuals who seem to suffer from chronic relapsing infection from Lyme disease?

Dr. Shulman. Individuals suffering from recurrent infections from the Lyme disease bacteria can be subject to a number of potentially serious clinical manifestations, including facial nerve weakness, headache, muscle pain, and arthritis. Fortunately, this outcome affects only a small minority of patients with Lyme disease. Research is targeted to identify the best treatments for the chronic forms of the disease.

WOMEN AND ARTHRITIS

Mr. Dwyer. More than 37 million Americans, or about one out of every seven, have some form of arthritis or other rheumatic disease. These diseases are the leading cause of mobility limitation. Does arthritis afflict women disproportionately? Do women suffer from some forms of arthritis exclusively?

Dr. Shulman. Some types of arthritis do afflict women disproportionately. Rheumatoid arthritis, systemic lupus erythematosus, and scleroderma, for example, are several times more common in women than men. The female to male ratio for systemic lupus erythematosus is nine to one. None of the rheumatic diseases, to my knowledge, affect women exclusively.

JUVENILE ARTHRITIS

Mr. Dwyer. What initiatives are currently underway to combat juvenile arthritis?

Dr. Shulman. Early diagnosis and appropriate therapy for juvenile arthritis are important to minimize deformity and disability. Testing for the rheumatoid factors, antinuclear antibodies, and certain tissue-type antigens greatly assist in

classifying young patients. There are several types of arthritis in children and their prognosis varies, as does their recommended treatment.

The discovery that juvenile arthritis is associated with several tissue-type antigens suggests a link with genetic factors. If susceptibility to the disease can be identified with a specific region of a particular gene, new therapeutic interventions may be possible in the future.

Mr. Dwyer. How much will NIAMS spend in fiscal year 1990 and 1991 on juvenile arthritis?

Dr. Shulman. The NIAMS plans to spend $561 thousand in FY 1990 and $575 thousand in FY 1991 on juvenile arthritis.

TRANSPLANTATION BIOLOGY

Mr. Dwyer. Has the advent of transplants and tissue typing improved diagnostic techniques for arthritis?

Dr. Shulman. The tissue typing used for transplantation has identified disease susceptibility in several different types of arthritis. These data may be helpful, but are not definitive for diagnosis of the individual patient.

Mr. Dwyer. Osteoporosis is responsible for approximately 1.3 million fractures each year. Estrogen depletion has been mentioned as a possible cause for osteoporosis. Has any research been conducted on the rate of osteoporosis vis-a-vis the extraordinary number of hysterectomies performed in the United States each year?

Dr. Shulman. Osteoporosis is characterized by low bone density and an increased risk of fracture. There has been extensive research on endocrine (female hormone) loss and osteoporosis. Bone mass decreases in all individuals as they age; women experience an acceleration of bone loss following menopause because of decreased levels of estrogen. A hysterectomy, if it involves the removal of the uterus and both ovaries, will precipitate menopause and thus exposes younger women who require this surgery to an increased risk of bone loss and osteoporosis. Hospital discharge data show the number of hysterectomies in 1988 as 578,000. Data from the National Center for Health Statistics, however, indicate a general reduction in the number of hysterectomies performed in the United States over the past few years.

A highly effective way to prevent bone loss in postmenopausal women is by estrogen replacement therapy (ERT). Estrogen also protects women from cardiovascular disease and may reduce their risk of heart attacks. The National Institute of Arthritis and Musculoskeletal and Skin Diseases has joined with several other institutes of the NIH to support a multi-centered clinical study to determine the best hormonal treatment regimen to optimize bone-sparing and cardiovascular effects of sex hormones while minimizing any other risks.

PRESCRIPTION DRUGS AND THE ELDERLY

Mr. Dwyer. Many elderly individuals suffer from arthritis in addition to other maladies such as hypertension. It is my understanding that many elderly people who suffer from arthritis are not able to avail themselves of effective treatment, because such treatment elevates blood pressure levels. What is currently being done to develop therapies, which can relieve the discomfort of arthritis without elevating blood pressure, or negatively interacting with other prescriptive drugs?

Dr. Shulman. Most of the currently available effective therapies for arthritis can be used by persons who suffer from rheumatic diseases without serious concern that such treatments might cause elevated blood pressure levels. Some agents, such as the corticosteroids, may cause edema and modest blood pressure elevation resulting from sodium and water retention. However, administration of a diuretic and a low sodium diet will allow continuation of therapy.

Hypertension itself can be well managed by the physician, together with the arthritis, without concern that serious consequences might arise. It is important that the physician be made aware of all medications being taken whether prescribed by other physicians or taken by the patient as self-medication with over-the-counter drugs. This approach will allow effective treatment for the arthritis and eliminate the possibility of negative interactions with other drugs.

RESEARCH TRAINING AND CAREER DEVELOPMENT

Mr. Conte. With the budgetary constraints and rising outside salaries, your Institute is facing severe problems in getting quality scientists. What is the impact of holding the line on research training and manpower programs? Are you concerned that the pool of qualified young investigators might decrease in the decade ahead?

Dr. Shulman. Maintaining a cadre of skilled scientific investigators is critical to the missions of the Institute. We are concerned about holding the line on research training and manpower development programs. The number of research trainees for FY 1991 will be supported at the same dollar level available in FY 1990. The FY 1991 request will support 52 research career development awards, a decrease of one award from FY 1990.

The current size of the pool of young investigators is insufficient to meet our future needs in light of the numerous exciting research opportunities facing the Institute over the next decade. The number of trainees has decreased significantly over recent years. Current levels are not sufficient to replace investigators that are being lost. Specifically, we need more young persons properly trained in the modern scientific methodologies of molecular biology and cell biology. Even more critical than the training positions is an expansion in research career manpower award programs. These provide in-depth development of research capabilities for success as independent investigators.

INTRAMURAL RESEARCH

Mr. Conte. As you know all too well, Dr. Shulman, space on the NIH campus is at a premium. How do you plan to use the additional intramural space that has been allotted to your institute?

Dr. Shulman. Some new space is expected to be available by the end of FY 1990, and this will be used to begin to house two new laboratories--the Laboratory of Skin Biology and the Laboratory of Structural Biology Research. Additional new space has been promised for 1 year later, and this will permit completion of our plans for the Laboratory of Skin Biology. Once these laboratories are set up, additional scientists will be recruited to staff these new efforts.

SPACE MEDICINE

Mr. Conte. Has anything been learned through research on bone disease and bone biology that may be of benefit to astronauts in space?

Dr. Shulman. A deficiency of mechanical loading on the bone causes a reduction in bone density. This loss of bone mass is true for bed-ridden patients or astronauts in a weightless environment. Bone biology research provides an understanding of the regulation of bone metabolism that may be applied to the biology of bones in space. Some of the research we support is directed specifically at the effects of mechanical forces on bone remodelling. In one study it is apparent that relatively small loads applied in a cyclic manner may be enough to stimulate bone to remodel in a normal way. This

approach may prove to be valuable for our astronauts. Another experimental approach has used electricity to rebuild bone in an animal model with low bone mass. This research may offer another means of restoring any bone mass lost by astronauts.

CONNECTIVE TISSUE DISEASES

Mr. Conte. As you noted in your opening statement, connective tissue disorders are among the most challenging diseases to treat. What new techniques are being developed to look at the underlying molecular causes of connective tissue diseases?

Dr. Shulman. Inborn disorders that impair the structure and development of the skeleton account for a significant fraction of the 12 million Americans who have birth defects. Underlying structural defects in the collagen molecule account for a significant portion of these disorders. The NIAMS is supporting a Workshop On Heritable Disorders of Connective Tissue at the National Institutes of Health, April 9-11, 1990. This workshop will bring together the leaders in this field to exchange ideas and to discuss future research directions.

A number of genetic and molecular biological techniques have been applied to the study of the collagen defects in these heritable connective tissue diseases: osteogenesis imperfecta, Marfan's syndrome, Ehlers-Danlos syndrome, and the chondrodysplasias. Collagen molecules form a scaffolding that supports the structure of bone and cartilage, as well as skin and other connective tissue throughout the body. The main thrust of the research is to understand how genetically determined changes in the structure of the collagen molecule affect its function.

Mr. Conte. Are you looking at genetic transfer processes in connective tissues diseases?

Dr. Shulman. Recently, investigators supported by the NIAMS have developed a unique animal model to study the structure-function relationship of the collagen molecule. Several human mutant collagen genes have been isolated and are available for study. These mutant human genes have been introduced into mice, which then synthesize and incorporate the defective collagen into connective tissue, thus allowing investigators to observe how the defects in genes are expressed in the animal's tissues. These animals, called transgenic mice because they carry foreign genes, constitute unique animal models for human genetic diseases caused by dominant mutations in the collagen genes.

Mr. Conte. You held a major conference last year on the effect of sunlight on the skin. Can you share with the Committee what were the major recommendations from the conference? What efforts are underway at your Institute to implement their recommendations?

Dr. Shulman. The Consensus Development Conference panel of experts has issued their final statement with recommendations regarding the prevention and treatment of the adverse effects of sunlight exposure and ultraviolet (UV) radiation on the skin. Among their findings and conclusions are the following:

- o UV radiation produces a variety of pathologic effects, including sunburn, pigmentary changes, immunologic alterations, and neoplasia.

- o The risk of UV radiation damage to the skin can be prevented or reduced by wearing proper clothing, using a physical or chemical sunscreen with a sun protection factor rating of at least 15, and modifying schedules of outdoor activities to avoid the peak exposure times between 10 a.m. and 3 p.m.

- o There is a need to better educate the public regarding the hazards of tanning parlors. There should be better regulation of tanning facilities to protect the public against unintentional exposure.

- o Sunlight-induced adverse skin alterations can be treated by standard surgical techniques and superficial modalities.

- o There is insufficient evidence at this time to recommend the use of Retin-A or similar compounds to treat or reverse the effects of sun damage on skin.

The Consensus Panel made a number of recommendations for further research on the effects of sunlight on the skin. The main recommendations were:

- o Further research to define the immunologic effects of UV radiation on the skin.

- o Additional research on the differences between sun-induced aging and chronologic aging.

- o The development of a more current database on the incidence of non-melanoma skin cancer.

- o Further research to define the action spectrum of sunlight and UV radiation in the pathogenesis of melanoma.
- o Further research on the biologic effects of UVA radiation particularly in regard to its "photoaging" and immunologic effects.

- o New approaches to diminish the risk of sun exposure in childhood and adolescence including such things as behavior modification and education.

- o The development of more effective sunscreens and the monitoring of the risk/benefit ratio of the widespread, long-term use of sunscreens.

NIAMS is preparing a program announcement highlighting the recommendations for further research made by the Consensus Panel. This will be coordinated with those other institutes at NIH whose area of interest include specific aspects of the recommendations.

INFLAMMATORY MUSCLE DISEASES

Mr. Conte. Tens of thousands of people are afflicted with painful inflammatory muscle diseases, like polymyositis and dermatomyositis. What are some of the possible triggers of inflammatory muscle diseases? Are there multiple causes for this condition? Does more work need to be done in the causes and treatment of these diseases? What are the future directions in research?

Dr. Shulman. Inflammatory myopathies, such as polymyositis and dermatomyositis, are characterized by pain, muscle weakness, and tissue damage. There are several apparent initiating factors for various types of myositis. There does not seem to be a common pattern in all cases; rather, there are several likely causes. There is an indication that viruses are associated with myositis. There is serologic evidence of recent prior coxsackie virus infection in many cases. This virus can produces inflammatory myopathy in certain animals. Picorna virus-like assemblies have been observed in some patients with myositis. In addition, myositis may be an early symptom in people with AIDS. Drugs and toxins are also implicated in certain inflammatory myopathies. Our intramural scientists are actively engaged in research on myositis along different fronts.

Myositis, both alone and in association with other conditions, is painful and can result in prolonged weakness and physical impairment. There is need for much additional work in both the causes and treatments of these diseases. There are very promising opportunities in further investigations of myositis induced by viruses.

RHEUMATOID ARTHRITIS

Mr. Porter. On page 238 of your budget justification you state that you will begin a clinical trial of minocycline for the treatment of rheumatoid arthritis. When will this trial begin? When will the results be available?

Dr. Shulman. The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) last summer issued requests for proposals, one for clinical centers, and the other for a coordinating center to participate in a clinical trial to assess the efficacy of minocycline in the treatment of rheumatoid arthritis. Proposals were received from institutions wishing to participate as clinical centers and five wishing to serve as the coordinating center for the study. These proposals have been reviewed by the NIAMS's review committee, and staff has prepared technical questions for the contracting office to use in negotiating with the prospective centers. The process is an iterative one, and the best and final offers will be made shortly. The NIAMS will then select the successful centers. It is anticipated that the contracts will be let this fiscal year.

The design of the study allows for a 6-month planning and organizational phase during which the protocol will be finalized, the manual of procedures and data forms will be created, and the study components will be trained and certified in the procedures of the

study. Recruitment of the volunteers is expected to take at least another 6 months, and all volunteers will be under treatment for at least 1 year. Data collection, and analysis and preparation of the final reports and publications will take another year. Therefore, we hope to be able to have the results of this study in the summer of 1993.

Mr. Porter. Assuming that minocycline is proven effective, the next step is development and evaluation of a form of tetracycline that retains the effectiveness of minocycline without its antibiotic properties. When do you expect that this second drug will be developed? How long will the evaluation of the new drug take? When do you expect the new drug to be generally available to individuals with rheumatoid arthritis?

Dr. Shulman. It is possible that there will be several derivatives of tetracycline that retain minocycline's collagenase inhibition properties but are not antibiotics. One such derivative, dedimethyl-amino-tetracycline, is a potent inhibitor of collagenase that lacks antibiotic effects. Researchers at the Long Island Jewish Medical Center and the State University of New York at Stony Brook are evaluating this derivative with an animal model of arthritis.

As to the issue of how long it will take to evaluate such new drugs, it depends upon how "new" they are. For example, if a non-antibiotic tetracycline is a well-known derivative or if its chemical structure is only slightly modified from a well known derivative, much of the preclinical testing for safety in animal models may not be necessary. If the desirable derivative represents a major modification, the preclinical testing required by the Food and Drug Administration (FDA) could take 2 to 4 years to complete. The required clinical testing (in humans) of a new drug typically takes an additional 3 to 5 years. The FDA usually requires at least two well-controlled clinical trials demonstrating efficacy of a drug before they will approve the labeling of a drug for a new indication. With all these unknowns, it is not possible to predict when such a new drug would be available for the treatment of rheumatoid arthritis.

LYME DISEASE

Mr. Porter. Are you coordinating with the NIAID in developing better diagnostic techniques for Lyme disease?

Dr. Shulman. As a result of the December 1988 scientific workshop, the NIAMS, in conjunction with the NIAID, issued a joint request for applications to encourage research in the pathogenesis of Lyme disease, including development of better diagnostic tests. The response to this announcement was gratifying, with 45 applications received. A number of these proposals dealt with methods to detect Lyme disease with greater accuracy and specificity. The review of these applications has just been completed, and the Institute expects to fund five excellent new proposals.

Mr. Porter. Are you coordinating on developing polymerase chain reaction (PCR) techniques?

Dr. Shulman. The diagnostic test for Lyme disease utilizing the polymerase chain reaction was developed by NIAID scientists in that Institute's Rocky Mountain Laboratories. We expect that researchers funded by both Institutes will participate in studies designed to bring this test to a practical reality.

Mr. Porter. When will adequate diagnostic tools be generally available?

Dr. Shulman. Diagnosis of Lyme disease is a very complex and difficult problem because the causative agent, Borrelia burgdorferi, generally cannot be directly observed or cultured from patients' specimens. Currently used laboratory tests have been shown to often lack sufficient sensitivity and specificity.

Several new tests are under development. One involves use of highly sensitive antibodies to detect the presence of bacteria in urine. Another uses the polymerase chain reaction to identify a a small quantity of bacteria in diseased tissues. A recent report described the ability to culture bacteria from the blood of patients with Lyme disease. Another recent study reports that the sensitivity of antibody tests can be increased by uncoupling immune complexes. These tests hold great promise for better diagnosis in the future.

RHEUMATOID ARTHRITIS

Mr. Porter. What is the status of your research into the role of mycoplasma in rheumatoid arthritis?

Dr. Shulman. The NIAMS currently supports three research projects related to the role of mycoplasma in arthritis including rheumatoid arthritis. Researchers at the University of Utah have had a long-standing grant from the NIAMS on this topic. They have been trying to determine how M. arthriditis mitogens (substances that induce cells to divide and lymphocytes to transform) may influence host susceptibility to diseases such as rheumatoid arthritis.

The second group at the University of South Dakota is studying the immune response in mycoplasma-induced arthritis. They are concentrating on the immunology of the host-parasite interactions at the level of the cell surface in hopes of identifying the major surface antigens involved in adherence to host tissues, resistance to phagocytosis (the process by which foreign material such as bacteria are ingested by macrophages), and virulence differences among strains of mycoplasma.

The third group is working at the University of Missouri on the organization and expression of mycoplasma genes. They are applying the modern techniques of molecular biology to determine the primary structure of membrane surface proteins of other species of mycoplasma that are arthritogenic, M. hyorhinis and M. hyopneumoniae. Although this research is not directly related to the pathogenesis of arthritis, understanding the molecular biology of mycoplasma will undoubtedly help direct future research in this area.

INFECTIOUS ETIOLOGY

Mr. Porter. In 1988, the NIAMS issued a program announcement encouraging applications to study infectious agents that might be involved in the development of rheumatoid arthritis and other forms of arthritis. You received at least 18 applications in response. How many applications were specific to the role of mycoplasma in rheumatoid arthritis? How many were funded? Of the total number of application received in response to the program announcement, how many were funded?

Dr. Shulman. Twenty-seven applications were received in response to the program announcement encouraging proposals to study infectious agents that might be involved in rheumatoid arthritis. Nine were specific to the role of mycoplasma in rheumatoid arthritis, and two of those were funded. Seven others relating to other infectious agents were funded. Thus, nine proposals were funded at a total cost of $1.2 million. The total support of the NIAMS for research on infectious agents is now $4.9 million.

Mr. Porter. Last year you told me that you are investigating possible links between Lyme disease and rheumatoid arthritis. What progress have you made in these investigations?

Dr. Shulman. Lyme disease and rheumatoid arthritis do have a number of similarities with respect to their arthritic manifestations. They may have similar underlying immunogenetic determinants.

BONE AND MINERAL DISEASES

Mr. Porter. Please provide for the record a listing of NIAMS-supported intramural and extramural research, and the level of funding, for each of the following areas--osteoporosis, primary hyperparathyroidism, steroid-induced bone disease, Paget's disease, nephrolithiasis, bone disease associated with renal failure (renal osteodystrophy), genetic disorders resulting in bone disease, and calcium disorders resulting in bone disease.

Dr. Shulman. As the lead agency for bone biology and bone diseases, NIAMS supports many grants in these areas. The tables below summarizes the specific information requested. The specific categories listed below do not reflect an additional portfolio of basic science projects that address bone biology, metabolism, growth, and structure. These additional efforts are the underlying science projects from which future applied advances may be developed.

Grant Support (FY 1989)	Number	Dollars
Osteoporosis - specific	69	$10,965,142
Primary hyperparathyroidism	--	---
Steroid-induced bone diseases	4	343,809
Paget's disease	1	151,706
Nephrolithiasis	1	68,176
Bone diseases from renal failure	--	---
Genetic bone diseases	8	846,852
Calcium disorders resulting in bone diseases	8	1,299,288

STEROID INDUCED BONE DISEASE

GRANT	INVESTIGATOR	TITLE	INSTITUTION	AWARD
P60 AR36834	Hahn, Ted	Glucocorticoid Reguation of Human Bone Cell Metabolism	University of California, Los Angeles	$ 66,687
P60 AR20621	Gronowicz, Gloria	Effect of Glucocorticoids on Bone Organ Culture	University of Connecticut Health Center	$ 71,017
P01 AR38933	Kream, Barbara	Glucocorticoids and Collagen on Bone Collagen	University of Connecticut Health Center	$ 82,086
R01 AR27850	Kream, Barbara	Normal Regulation of Bone Collagen Metabolism	University of Connecticut Health Center	$124,019
PAGET'S DISEASE OF BONE				
R01 AR19980	Mills, Barbara	Study of Possible Causes of Paget's Disease of Bone	University of Southern California	$151,706
NEPHROLITHIASIS				
R01 AR16061	Pak, Charles	Theoretical and Tnerapeutic Aspects of Calification	University of Texas SW Medical Center, Dallas	$68,176

GENETIC DISORDERS RESULTING IN BONE DISEASE

GRANT	INVESTIGATOR	TITLE	INSTITUTION	AWARD
R01 AR30426	Rowe, David	Type I Collagen mRNA In Osteogenesis Imperfecta	University of Connecticut Health Center	$162,256
R01 AR37042	Cheung, David	Collagen Structure and Crosslinking In O.I Bone	University of Southern California	$ 96,311
R01 AR37318	Eyre, David	Pathology of Inborn Skeletal Diseases	University of Washington	$181,966
R01 AR37318	Eyre, David	Pathology of Inborn Skeletal Diseases	University of Washington	$ 35,336
R01 AR38473	Bonadio, Jeffrey	Molecular Basis Of Osteogenesis Imperfecta Type II	University of Michigan at Ann Arbor	$ 59,860
R01 AR38474	Wenstrup, Richard	Molecular Mechanisms in Mild Osteogenesis Imperfecta	Duke University	$ 92,042
R01 AR39837	Cohn, Daniel	Genetic and Molecular Basis Of Osteogenesis Imperfecta	Cedars-Sinai Medical Center	$ 91,169
R01 AR39870	Shapiro, Jay	Collagen Metabolism In O.I. Osteoblasts	St. Vincent Hospital (Worcester, MA)	$127,912

CALCIUM DISORDERS RESULTING IN BONE DISEASE

GRANT	INVESTIGATOR	TITLE	INSTITUTION	AWARD
R01 AR37520	Aloia, John	Prevention of Postmenopausal Bone Loss	Winthrop-University Hospital	$ 84,557
P01 AR32087	Avioli, Louis	Calcium Transport, Bone Cell Function, and Aging	Jewish Hospital of St. Louis	$489,365
T32 AR07048	Deftos, Leonard	Diseases of Bone and Calcium Metabolism	University of California, San Diego	$ 57,478
R01 AR27032	Drezner, Marc	Pathogenesis of Vitamin D Refractory of Diseases	Duke University	$ 61,781
R01 AR27032	Drezner, Marc	Pathogenesis of Vitamin D Refractory of Diseases	Duke University $320,199	
R01 AR07912	Heaney, Robert	Longitudinal Study of a Pre-Osteoporosis Population	Creighton University	$121,246
R01 AR15781	Haussler, Mark	Function of Vitamin D Metabolites and Bone Diseases	University of Arizona	$ 75,636
R01 AR36903	Lobaugh, Bruce	Control of Calcium Metabolism in Aging and Osteoporosis	Duke University	$ 89,026

OSTEOPOROSIS

GRANT	INVESTIGATOR	TITLE	AWARD
K11 AR01793	Dedrick, Dale	Travecular Bone Physiologic Response to Applied Stress	18,439
T32 AR07033	Avoli, Louis	Mineral and Skeletal Metabolism	34,593
T32 AR07543	Baylink, David	Research Training in Biomedical Studies of Bone	16,185
R01 AR07912	Heaney, Robert	Longitudinal Study of a Pre-Osteoporosis Population	363,740
F32 AR08031	Harrison, John	Hormonal Regulation of Collagen Gene Expression in Bone	14,000
R01 AR15781	Haussler, Mark	Function of Vitamin D Metabolites and Bone Disease	56,727
R01 AR16061	Pak, Charles	Theoretical and Therapeutic Aspects of Calcification	204,530
P60 AR20613	Meenan, Robert	Multipurpose Arthritis Center	177,861
P60 AR20621	Rothfield, Naomi	Multipurpose Arthritis Center	116,904
R01 AR27065	Riggs, Byron	Epidemiology of Age-Related Bone Loss and Fractures	218,726
R01 AR27926	Genant, Harry	Quantitative Tomography For Bone Mineral Assessment	130,873
R01 AR28576	Riggs, Lawrence	Fluoride and Calcium Treatment For Osteoporosis	166,977
R01 AR28583	Kleerekoper, Michae	Safety and Efficacy of Fluoride Therapy in Osteoporosis	153,091
R01 AR31062	Bbaylink, David	Endosteal Bone Volume Regulation and Osteoporosis	163,867
P01 AR32087	Avioli, Louis	Calcium Transport, Bone Cell Function, and Aging	244,682
R01 AR33066	Edwards, Thomas	Biomechanics of Vertebral Fractures in Osteoporosis	128,332
R01 AR33667	Haughton, Victor	A CT, MR and Cryomicrotomic Study of Spine Anatomy	158,173
R01 AR34399	Goldstein, Steven	Trabecular Architectural Effects on Material Properties	42,387
R01 AR35582	Kuller, Lewis	Risk Factors For Hip and Colles' Fractures	284,945
R01 AR35583	Vogt, Thomas	Risk Factors For Hip and Colles' Fractures	368,085
R01 AR35584	Sherwin, Roger	Risk Factors For Hip and Colles' Fracture	248,749
R01 AR35651	Turner, Russell	Bone and Mineral Homeostatis in Immobilization	114,477
R01 AR35858	Kuller, Lewis	Epidemiology of Hormones and Osteoporosis	172,969
R01 AR36066	Bell, Norman	Bone and Mineral Metabolism in Blacks and Whites	137,183
R01 AR36257	Ashman, Richard	Atlas of Human Bone Mechanical Properties	11,785
R01 AR36384	Schlechte, Janet	Hyperprolactinemic Amenorrhea and Osteopenia of Aging	100,624
R01 AR36903	Lobaugh, Bruce	Control of Calcium Metabolism in Aging and Osteoporosis	89,026

GRANT	INVESTIGATOR	TITLE	AWARD
R01 AR37078	Gorski, Jeffrey	Proteoglycan Turnover by Osteoblast-Like Cells	28,799
R44 AR37189	Boyd, Douglas	A High-Speed DPA Scanner For Diagnosis of Osteoporosis	306,893
R01 AR37520	Aloia, John	Prevention of Postmenopausal Bone Loss	169,114
R01 AR37562	Genant, Harry	Enhancement of Peak Bone Mass in Young Women	206,577
R01 AR38346	Jee, Webster Shew	Making New Bone Trabeculae in Osteopenic Aged Skeleton	143,187
P60 AR38520	Christian, Charles	Multipurpose Arthritis Center	105,284
R29 AR38869	Cheal, Edward	Interfragmentary Strain Hypothesis and Fracture Healing	49,596
R01 AR38874	Flynn, Michael	In-Vivo Vertebral Bone Architecture in Osteoporosis	154,008
P01 AR38933	Raisz, Lawrence	Pathogenesis and Prevention of Osteoporosis	682,380
P01 AR38933	Raisz, Lawrence	Pathogenesis and Prevention of Osteoporosis	56,391
R01 AR38941	Marcus, Robert	Exercise Intensity & Bone Mass in Young Women	192,603
P50 AR39191	Lindsay, Robert	Specialized Center of Research in Osteoporosis	719,639
R29 AR39201	Centrella, Michael	Bone Collagen Production by Bone-Derived TGFB	5,360
R01 AR39215	Goodsitt, Mitchell	Analysis of Mineral and Fat Content by Quantitative CT	83,248
P50 AR39221	Recker, Robert	Specialized Center of Research in Osteoporosis	838,789
P50 AR39226	Brighton, Carl	Interaction of Hormones and Physical Stress on Bone Mass	834,255
R01 AR39234	Sandler, Rivka	Muscle Strength and Postmenopausal Bone Loss	225,775
R01 AR39241	Luben, Richard	Bone Cell Antigens Related to PTH Receptors	40,126
R01 AR39245	Muallem, Shmuel	HCO3-Secretion & Cell Volume Regulation by Osteoblasts	12,892
R29 AR39278	Rubin, Clinton	Attenuation of Wolff's Law by Systemic Disorders	86,093
R01 AR39357	Bonewald, Lynda	Mechanisms of TGFB Activation in Bone Micro-Environment	9,267
R01 AR39514	Pertschuk, Michael	Longitudinal Study of Bone Density in Anorexia Nervosa	66,694
R01 AR39559	Lohman, Timothy	Effects of Exercise on Bone Mineral Content in Women	426,126
R43 AR39601	Jenny, Richard	Immunoassay For Osteocalcin Fragments	11,534
R01 AR39623	Chambers, Timothy	Investigate the Regulation of Bone Resorption	58,584
R29 AR39651	Powers, Mary	Effect of Lactation on Bone	44,978
R01 AR39657	Kleerekoper, Michae	Biochemical Markers and Bone Loss in Older Women	374,399
P01 AR39674	Lazarus, Gerald	Proteinases and Mediators in Cutaneous Biology	264,589
R01 AR39743	Partridge, Nicola	Parathyroid Hormone Regulation of Osteoblastic MNRA	31,614
R01 AR39760	Hayes, Wilson	Multiscan Photon Absorptiometry & Osteoporotic Fracture	151,997
R01 AR39794	Bauer, Richard	Osteoporosis in Mexican Americans and Nonhispanic Whites	145,583
R01 AR40073	Horowitz, Mark	Mechanisms of Osteoblast Activation and Regulation	40,838

GRANT	INVESTIGATOR	TITLE	AWARD
Y02 AR90009	Feinleib, Manning	NHANES III: Collaborative Study	50,000
Y02 AR90012	Feinleib, Manning	NHANES II and NHANES III: Digitization of X-ray Films.	50,000
U01 HL40154	Pauerstein, Carl	Postmenopausal Estrogen/Progestin Interventions	23,755
U01 HL40185	La Rosa, John	Postmenopausal Hormone Therapy--Risks and Benefits	26,658
U01 HL40195	Schrott, Helmut	Postmenopausal Estrogen/Progestin Interventions	16,578
U01 HL40205	Wood, Peter	Stanford Postmenopausal Hormone Replacement Study	22,624
U01 HL40207	Barrett-Connor, Eli	Postmenopausal Estrogen/Progestin Interventions	16,453
U01 HL40231	Bush, Trudy	Postmenopausal Estrogen/Progestin Clinical Center	18,348
U01 HL40232	Wells, Bradley	Postmenopausal Estrogen/Progestin Coordinating Center	58,439
U01 HL40273	Judd, Howard	Estrogen and Progestin in Heart Disease	17,145
Z01 AR41077	Bolander, Marc	Regulation of Gene Expression in Normal & Impaired Fracture	160,000

Mr. Porter. Do you have any data on the frequency of these diseases? If so, would you provide them for the record.

Dr. Shulman. Data on the frequency of bone and mineral diseases are not uniformly available. The following are the best available data for the diseases that you mention.

Osteoporosis: Osteoporosis, a condition in which bone mass is reduced and there is an increased susceptibility to fractures, is a major public health problem in the United States. It affects more than 24 million people in the United States and is responsible for at least 1.3 million fractures each year, typically fractures of the spine, wrist, and hip.

Primary Hyperparathyroidism: Approximately 0.5 percent of the U.S. population is affected by primary hyperparathyroidism.

Steroid-Induced Bone Disease: To our knowledge, no reliable data are available on the frequency of steroid-induced bone disease.

Paget's Disease: To our knowledge, reliable figures are not available on the frequency of Paget's disease in the United States. Surveys in England and Germany have provided estimates of the prevalence rate of Paget's disease in individuals over 40 years of age to be approximately 3 to 4 percent.

Bone Diseases Associated With Renal Failure (Renal Osteodystrophy): No data are available on the frequency of bone disease associated with renal failure (renal osteodystrophy).

Nephrolithiasis: An estimated 4 percent of the U.S. population will experience nephrolithiasis (kidney stones) in their lifetime.

Genetic Disorders Resulting in Bone Disease: Congenital malformations of the musculoskeletal system are diagnosed among live births and stillbirths more frequently than defects of any other organ system. Estimates of prevalence rates for all musculoskeletal conditions, diagnosed at birth, range from 3 to 10 percent depending on whether minor anomalies are counted, as well as major abnormalities.

Osteogenesis imperfecta is one of the major genetic diseases of children. It causes fragile bones with premature bone fractures, and additional defects in other organs that consist of connective tissues. As estimated 30,000 people in the United States are afflicted with osteogenesis imperfecta.

Calcium Disorders Resulting in Bone Disease: Other disorders of bone and mineral metabolism have been identified. These include osteopetrosis and pediatric osteoporosis. Estimates of their frequency are not available.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

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NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

For carrying out section 301 and title IV of the Public Health Service Act with respect to arthritis and musculoskeletal and skin diseases [$171,681,000] $176,080,000.

(Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 1990.)

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Amounts Available for Obligation 1/

	1989 Actual	1990 Appropriation	1991 Estimate
Appropriation	$161,931,000	$171,681,000	$176,080,000
Enacted administrative reduction	-2,034,000	-431,000	
Sequester Order		-2,320,000	
Subtotal, adjusted appropriation	157,897,000	168,930,000	176,080,000
Real transfer to the Office of the Assistant Secretary for AIDS research for AZT	-6,000		
Comparative transfer to: Division of Research Resources for administrative costs of the RCMI program	-5,000		
Comparative transfer to:			
Office of Research Services to Fogarty International Center for Passport Activity	-3,000	-3,000	
Comparative transfer from:			
Office of the Director for FTE increase	197,000		
Subtotal, adjusted budget authority	160,080,000	168,927,000	176,080,000
Unobligated balance, lapsing	-5,000		
Total, obligations	160,075,000	168,927,000	176,080,000

1/ Excludes the following amounts for reimbursable activities carried out under this account: 1989 -- $1,543,000; 1990 -- $1,870,000; 1991 -- $1,970,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Budget Mechanism

(Dollars in thousands)

	1989 Actual		1990 1/ Appropriation		1991 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Grants						
Research projects:						
Noncompeting	471	$77,471	508	$89,662	494	$87,610
Administrative supplemental	(3)	157	(10)	337	(10)	342
Competing:						
Renewal	64	13,698	59	11,387	66	14,520
New	118	16,535	74	10,950	82	15,683
Supplemental	3	311	2	174	2	174
Subtotal, competing	185	30,544	135	22,511	150	30,377
Subtotal, research projects	656	108,172	643	112,510	644	118,329
Research centers:						
Specialized/ Comprehensive centers	26	21,401	26	21,025	26	21,025
Other Research:						
Research career programs	52	3,315	53	3,434	52	3,349
Minority biomedical research support		331		337		366
Other research related	27	1,943	21	2,012	21	2,012
Subtotal, other research	79	5,589	74	5,783	73	5,727
Total, research grants	761	135,162	743	139,318	743	145,081

Training						
Individual awards						
Noncompeting.....	12	394	16	440	28	766
Competing:						
Renewal.....	0	0	0	0	0	0
New.....	17	417	21	571	9	245
Subtotal, individual.....	29	811	37	1,011	37	1,011
Institutional awards						
Noncompeting.....	161	4,610	140	4,225	147	4,557
Competing:						
Renewal.....	27	902	42	1319	36	1030
New.....	2	79	6	187	5	144
Subtotal, institutional....	190	5,591	188	5,731	188	5,731
Total, training.....	219	6,402	225	6,742	225	6,742
Research and development contracts....	11 FTE	2,996	11 FTE	3,702	11 FTE	3,692
Intramural research.....	53	9,694	57	12,077	61	12,922
Research management and support.....	60	5,826	59	6,724	61	7,643
Extramural Construction.....				364		
TOTAL BUDGET AUTHORITY...	113	160,080	116	168,927	122	176,080
HIV/AIDS	(2)	(733)	(3)	(1,238)	(4)	(1,483)

1/ Includes approximately $364,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

CROSSWALK - 1989 Actual
(Dollars in thousands)

PROGRAM ACTIVITY	MECHANISM								
	Research Grants			Training Programs		Research and Development Contracts	Intramural Research	Research Management and Support	Total
	Research Projects	Research Centers	Other Research	Individual	Institutional				
Arthritis, Musculoskeletal and Skin Diseases.....	$108,172	$21,401	$5,589	$811	$5,591	$2,996			$144,560
Intramural Research.							$9,694		$9,694
Research Management and Support.....								$5,826	5,826
Total Budget Authority	108,172	21,401	5,589	811	5,591	2,996	9,694	5,826	160,080

National Institute of Arthritis and Musculoskeletal and Skin Diseases

CROSSWALK - 1990 Appropriation 1/
(Dollars in thousands)

PROGRAM ACTIVITY	MECHANISM									
	Research Grants			Training Programs		Research and Development Contracts	Intramural Research	Research Management and Support	Extramural Construction	Total
	Research Projects	Research Centers	Other Research	Individual	Institutional					
Arthritis, Musculoskeletal and Skin Diseases.....	$112,510	$21,025	$5,783	$1,011	$5,731	$3,702				$149,762
Intramural Research.							$12,077			12,077
Research Management and Support.....								$6,724		6,724
Extramural Construction									364	364
Total Budget Authority	112,510	21,025	5,783	1,011	5,731	3,702	12,077	6,724	364	168,927

1/ Includes approximately $364,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

29-452 O—90—15

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

CROSSWALK - 1991 Estimate
(Dollars in thousands)

PROGRAM ACTIVITY	MECHANISM								
	Research Grants			Training Programs		Research and Development Contracts	Intramural Research	Research Management and Support	Total
	Research Projects	Research Centers	Other Research	Individual	Institutional				
Arthritis, Musculoskeletal and Skin Diseases.....	$118,329	$21,025	$5,727	$1,011	$5,731	$3,692			$155,515
Intramural Research.							$12,922		12,922
Research Management and Support.....								$7,643	7,643
Total Budget Authority	118,329	21,025	5,727	1,011	5,731	3,692	12,922	7,643	176,080

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Summary of Changes

1990 Estimated budget authority	$168,927,000
1991 Estimated budget authority	176,080,000
Net Change	+7,153,000

Changes:	1990 Current Estimate Base Pos. (FTEs)	1990 Current Estimate Base Amount	Change from Base Pos. (FTEs)	Change from Base Amount
A. Built-in:				
1. FY 1991 pay raise		$6,495,000		$295,000
2. Annualization of 1990 pay increases		6,495,000		+89,000
3. Within grade increases		6,495,000		+77,000
4. One day extra pay		6,495,000		+26,000
5. Federal Employees Compensation Fund Increase		21,000		+1,000
6. FTS rate increase		52,000		+2,000
7. Payment for centrally furnished services		7,118,000		+883,000
8. Increased cost of laboratory supplies, materials, and other expenses		5,191,000		+123,000
9. DHHS Working Capital Fund		157,000		-8,000
Subtotal				+1,488,000
B. Program:	No.	Amount	No.	Amount
1. Research projects:				
a. Noncompeting	508	89,991,000	-14	-2,047,000
b. Competing	135	22,408,000	+15	+7,866,000
Total	643	112,510,000	+1	+5,819,000
2. Other research	74	5,783,000	-1	-56,000
3. Research contracts		3,702,000		-10,000
4. Additional FTEs	Pos. (FTEs) 116	6,495,000	Pos. (FTEs) +6	+276,000
5. Extramural construction		364,000		-364,000
Subtotal				+5,665,000
Total changes				+7,153,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Budget Authority by Activity

(Dollars in thousands)

	1989 Actual 1/		1990 Appropriation		1991 Estimate	
	FTEs	Amount	FTEs	Amount	FTEs	Amount
Arthritis and musculoskeletal and skin diseases.....		$144,560		149,762		155,515
Intramural research....	53	9,689	57	12,077	61	12,922
Research management and support.....	60	5,826	59	6,724	61	7,643
Extramural Construction.....				364		
Total, obligations	113	160,075	116	168,927	122	176,080
Unobligated balance lapsing.....		5		---		---
Total, Budget Authority	113	160,080	116	168,927	122	176,080
HIV/AIDS	(2)	(733)	(3)	(1,238)	(4)	(1,483)

1/ The 1989 actual excludes a real transfer of $6,000 to the Health Resources and Services Administration for AZT grants; a comparable transfer of a comparable transfer of $5,000 to the Division of Research Resources for administrative costs of the RCMI program; and a comparable transfer from the Office of the Director for FTE increases.

2/ Includes approximately $364,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Budget Authority by Object

	1990 Appropriation	1991 Estimate	Increase or Decrease
Full-time equivalent of permanent positions	90	96	+6
Total compensable workyears: Full-time equivalent employment	118	124	+6
Full-time equivalent of overtime and holiday hours	1	1	---
Average ES salary	81,430	98,856	+17,426
Average GM/GS grade	9.5	9.5	---
Average GM/GS salary	39,753	41,184	+1,431
Average salary, grades est. by act of July 1, 1944 (42 USC 207)	79,421	82,280	+2,859
Average salary of ungraded positions	19,635	20,342	+707
Personnel Compensation:			
Full-time permanent	3,604,000	3,991,000	+387,000
Other than full-time permanent	1,364,000	1,442,000	+78,000
Other personnel compensation	210,000	218,000	+8,000
Special personnel services	370,000	375,000	+5,000
Subtotal, personnel compensation	5,548,000	6,026,000	+478,000
Personnel benefits	940,000	1,033,000	+93,000
Benefits for former personnel	7,000	12,000	+5,000
Travel and transportation of persons	249,000	265,000	+16,000
Transportation of things	15,000	18,000	+3,000

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	1990 Appropriation	1991 Estimate	Increase or Decrease
Rent, communications and utilities...	185,000	197,000	+12,000
Printing and reproduction.....	95,000	108,000	+13,000
Other Services:			
Project contracts.....	3,702,000	3,692,000	-10,000
Centrally furnished services.....	7,118,000	8,001,000	+883,000
Standard level user charge.....	0	0	0
Other.....	2,476,000	2,625,000	+149,000
Supplies and materials.....	1,636,000	1,703,000	+67,000
Equipment.....	532,000	577,000	+45,000
Grants, subsidies and contributions..	146,424,000	151,823,000	+5,399,000
TOTAL.....	168,927,000	176,080,000	+7,153,000

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Significant Items in House Appropriations Committee Reports

Item	Action Taken or to be taken
1990 House Report	
1. "The Committee continues to be impressed with the ability of the Institute's [NIAMS] grants program to attract very high quality research proposals. However, the Committee is concerned with the disparity between the continued high quality of applications in arthritis and musculoskeletal and skin diseases, and the low funding cutoff for the Institute relative to other NIH institutes." (p. 78)	1. The quality of NIAMS grant applications continues at a very high level. The 1989 funding level was again among the lowest at the NIH. Funding for research project grants was increased in fiscal year 1990, but because of the large number of continuation projects the Institute will award only 135 competing grants, a drop of 50 from 1989.
2. "The Committee applauds the NIAMS for its recent program announcements on the infectious etiology of arthritis, and on antibiotic therapies for arthritis. The Committee encourages the NIAMS to continue to expand its investigation of the possible link between rheumatic disease and a number of infectious agents including mycoplasmas." (p. 79)	2. In fiscal year 1989, NIAMS spent $4.9 million for investigations related to the possible link between rheumatic disease and a variety of infectious agents, including bacteria, viruses, and mycoplasma. Funding for this research will increase in fiscal year 1990. Later this year, the Institute will begin a multicentered clinical trial to test the efficacy and safety of minocycline in treating rheumatoid arthritis.
3. "Systemic Lupus Erythematosus (lupus) is an immune-related disease that affects the body's organs in various combinations. The vast majority of people with lupus, about 90 percent, are women in the child bearing age. Lupus is three times more likely in Black women than in white women. The Committee urges the National Institute of Arthritis	3. Research on systemic lupus erythematosus continues to be a major focus of research both in the extramural program and the intramural program. Survival has improved. Focus is now on helping the patient live a more normal life. Pregnancies are now possible. Specific antibodies help predict fetal outcome. Details of the

Item	Action Taken or to be Taken
and Musculoskeletal and Skin Diseases to continue its active support for research on this disease." (p. 79)	heredity nature of the illness are now known but many questions remain. Lupus has become better recognized, and diagnostic tests, such as antibody to DNA and Sm antigen and serum complement components, are providing important markers that allow physicians to target management of the disease to the individual patient.
4. "The Committee is interested in the scientific progress being made in our understanding of bone and mineral-related diseases which affect millions of Americans, both young and old alike, ranging from congenital disease to osteoporosis and Paget's disease. The Committee is aware of increasing research opportunities into the causes, prevention and treatment of such diseases and requests that the Institute specifically address this issue in its 1991 budget submission and that it be prepared to testify on this matter at the hearings." (p. 80)	4. Research on the structure of bone and mineral metabolism is an area of active research progress. The biological bases for osteoporosis are now better understood. NIAMS-supported studies have refuted the usefulness of a commonly used therapy, and have suggested alternative therapies. In Paget's disease, the different roles of bone formation in resorption are better understood. Studies are investigating the potential role of viral infection in causing this illness.
5. "The Committee is pleased with the direction that the Director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases is taking with regards to planning a research program to investigate alopecia areata, and its related diseases. The Committee is well aware that over two million people suffer from this condition, and that the Director's initiative to convene a special symposium is an excellent first step." (p. 80)	5. In April of 1989, the NIAMS convened a meeting of experts to review the state of the science of normal and abnormal growth of hair with specific reference to alopecia areata, and to advise the Institute on future research directions and ways to encourage and generate additional research in this area. During 1990, we plan to hold a scientific workshop on the many issues related to alopecia.

Item	Action Taken or to be Taken
6. "Once again, the Committee has heard compelling testimony about the devastating effects of epidermolysis bullosa (EB), a severely painful and debilitating inherited skin disease that resembles third-degree burns.... The Committee continues to be concerned about the complex nature of EB and its impact on its victims, their families and society. The problems of EB are those of genetics, development and differentiation, wound-healing, tissue-tissue interactions, mucous membrane involvement, internal organ systems, carcinogenesis, and undoubtedly many more. A largely unexplored, but very promising area of focus in EB research, is the use of genetic mapping both to identify the genes for the various types of EB and at a more clinical level to identify individuals at risk for carrying these genes.... In view of the medical, emotional and financial burden caused by EB, the Committee encourages the Institute [NIAMS] to strengthen and support a multidisciplinary research effort that will more effectively deal with the problem of EB." (p. 80/81)	6. The Institute is pleased with the progress that has been made in establishing the Epidermolysis Bullosa Disease Registry. Recently, scientists have discovered that certain inbred sheep manifest the characteristics of recessive dystrophic EB, one of its most severe forms. The emergence of such an animal model of this human disease opens new avenues of research, including the ability to conduct drug intervention studies more easily. Using patients and patients' families identified through the registry, investigations of EB utilizing modern methods of molecular genetics are being pursued. Plans are also being developed for using this important resource for additional clinical studies of various forms of EB.

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National Institute of Arthritis and Musculoskeletal and Skin Diseases

Significant Items in Senate Appropriations Committee Reports

Item	Action Taken or to be taken
1990 Senate Report	
1. "Rheumatoid arthritis -- The Committee is pleased with the NIAMS request for proposals for the medical community concerning clinical centers for an assessment of the efficacy of minocycline in the treatment of rheumatoid arthritis at multiple sites over a 5-year time period. The Committee is very interested in seeing the results of intravenous antibiotics as well as oral antibiotics. The Committee is especially interested in seeing 5 year results." (p. 149)	1. NIAMS plans a multi-center clinical trial of minocycline therapy for one year or more in 200 volunteers with rheumatoid arthritis. Awarding of contracts is expected by June 1990. Results of the trial should be available in 1993. Minocycline inhibits the activity of collagenase--an enzyme that breaks down the major protein component of connective tissue in cartilage and bone. The trial is based on the hypothesis that inhibiting collagenase activity in patients with rheumatoid arthritis will prove beneficial by blocking the destruction of cartilage, bone and other connective tissue joint structures.
2. "The Committee is aware that the mycoplasma organism has been suggested as the infectious agent responsible for rheumatic diseases in humans. The Committee recommends that the NIAMS support research to determine the role of mycoplasma in humans in triggering rheumatoid arthritis and other rheumatic diseases..." (p. 149/150)	2. NIAMS is interested in possible infectious causes of rheumatoid arthritis and other rheumatic diseases. In fiscal year 1989, the Institute spent $4.9 million on research concerned with the infectious etiology of rheumatic diseases. We currently support 31 such projects; of which three are concerned primarily with research on mycoplasma. In February 1988, NIAMS issued a Program Announcement to stimulate a more intensive search for infectious agents as initiating or contributing factors to the development of rheumatic diseases. Several new applications have been submitted, and they are now under consideration.

Item	Action Taken or to be Taken
3. "Systemic lupus erythematosus -- Research efforts will continue with fiscal year 1990 funding on systemic lupus erythematosus, or lupus... The Committee urges that NIAMS support an expanded lupus research program." (p. 150)	3. Research on lupus is a major focus in both the extramural research programs and the intramural research programs. Scientists are continuing to attack lupus on a number of fronts; the accomplishments of this program have been significant. As the lead Institute for research on lupus, NIAMS convened the Lupus Erythematosus Coordinating Committee. The report of the committee outlined the wide range of research opportunities available to scientists for studying lupus. These opportunities are being pursued. In 1989, NIAMS allocated $11.8 million for research on lupus, and that effort will continue as new projects are reviewed and approved. NIAMS plans to sponsor a scientific workshop in 1991 to assess current knowledge and formulate additional research directions.
4. "Scleroderma -- ... The Committee expects that the very highest priority be given to expanding scleroderma research with the additional funds provided by the Committee." (p. 151)	4. Scleroderma is a disease that results from overproduction of collagen, the basic element of the body's connective tissue. The cause of scleroderma is unclear. The most common first symptom of scleroderma is Raynaud's phenomenon, blanching of fingers and toes due to spasm of small blood vessels on exposure to cold. Specific autoantibodies are associated with this disease. A promising animal model of scleroderma has been recently developed. With this model, it should be possible to elucidate the events responsible for increased accumulation of collagen in the skin. We are encouraging research on the vascular connective tissue and immunologic abnormalities of scleroderma.

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Item	Action Taken or to be Taken
5. "Epidermolysis bullosa [EB] -- The Committee is pleased to learn that over the past two years large numbers of patients have been enrolled in the National EB Registry and that efforts at the NIAMSD are now underway to analyze the data. New areas of inquiry, such as the use of genetic mapping, both to identify the gene for various types of EB and to identify individuals at risk for carrying these genes, are very promising areas for focus in EB research. The Committee remains concerned about the complex nature of the disease and the need for the NIAMSD to establish and support a multidisciplinary research effort that will more effectively deal with the problems of EB. Furthermore, the Committee continues to believe that specialized centers of research have proven to be a successful mechanism in addressing the multidisciplinary needs of other genetic diseases and encourages the NIAMS to plan for the establishment of a limited number of these centers for EB and other catastrophic skin diseases." (p. 151)	5. NIAMS is pleased with the progress that has been made in establishing the Epidermolysis Bullosa Disease Registry. Plans are being developed for the futher utilization of this important resource in clinical studies of the various forms of EB. The Institute has had long-standing plans, developed with advice of leaders in dermatologic research, to provide a total of six Skin Diseases Research Centers; budget limitations have permitted the establishment of only two such centers. These centers would be an important resource for multidisciplinary research on EB and other catastrophic skin diseases.
6. "Advances on skin research -- ... The Committee is impressed by the rapid development of research in dermatology, especially as researchers in that field are taking advantage of the work being done in the areas of molecular and cellular biology and immunobiology. The skin disease research centers, which are contributing to these advances, should be adequately funded in fiscal year 1990." (p. 152)	6. The Institute, developed with advice of leaders in dermatologic research, has had long-standing plans to provide a total of six Skin Diseases Research Centers; budget limitations have permitted the establishment of only two such centers. All research centers, including the two Skin Diseases Research Centers, have been constrained in recent years in order to stretch the limited research dollars to cover all the Institute priorities.

Item	Action Taken or to be Taken
7. "Heritable disorders of connective tissue -- The Committee urges the National Institute of Arthritis, Musculoskeletal and Skin Diseases to sponsor a heritable disorders of connective tissue workshop during 1990. This symposium will allow basic scientists and clinicians working on these disorders to discuss current research and treatment initiatives. Within available funding, the Committee urges the NIAMS to expand its research effort in this area." (p. 152)	7. NIAMS has organized a broad-based scientific workshop on heritable disorders of connective tissue to be held on April 9-11, 1990. This area is important to all the major components (arthritis and musculoskeletal and skin diseases programs) of the Institute. New research will be supported within available funds.
8. "The Committee is aware and pleased that the Multipurpose Arthritis and Musculoskeletal Diseases Centers Programs of NIAMS are expected to be especially amenable to clinical nursing research areas. The Committee is especially pleased that NIAMS encourages nurses to submit research proposals in these areas, and urges NIAMS to continue these efforts to ensure involvement of professional nurses in its programs and activities." (p. 152)	8. NIAMS is fortunate to have a number of productive nurse investigators and allied health professionals involved in the programs of the Institute. The Multipurpose Arthritis and Musculoskeletal Disease Centers, in particular, provide an important focus for the activities of these investigators. A representative from the National Center for Nursing Research serves on two important coordinating committees chaired by the Institute director, and nurses have been serving on our advisory council and board.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1990 Amount Authorized	1990 Appropriation	1991 Amount Authorized	1991 Budget Estimate
Research and Investigation.....	Section 301	42 § 241	Indefinite		Indefinite	
National Institute of Arthritis and Musculoskeletal and Skin Diseases.....	Title IV	42 § 285d	Indefinite		Indefinite	
National Institute of Arthritis and Musculoskeletal Disease Programs.....	Title IV	42 § 285d-1	Indefinite		Indefinite	
Research and Training.....	Title IV	42 § 285d-2	Indefinite		Indefinite	
Data System and Information Clearinghouse.....	Title IV	42 § 285d-3	Indefinite	$162,185,000	Indefinite	$169,338,000
Interagency Coordinating Committees.....	Title IV	42 § 285d-4	Indefinite		Indefinite	
Arthritis and Musculoskeletal Diseases Demonstration Programs..	Title IV	42 § 285d-5	Indefinite		Indefinite	
Multipurpose Arthritis and Musculoskeletal Diseases Centers	Title IV	42 § 285d-6	Indefinite		Indefinite	
Advisory Board.....	Title IV	42 § 285d-7	Indefinite		Indefinite	
National Research Service Awards...	Title IV Part F	42 § 288	Such sums as necessary. 1/	6,742,000	Authorizing Legislation to be requested. 1/	6,742,000
Total Budget Authority.....				168,927,000		176,080,000

1/ This training authority is shared with other research training programs of the National Institutes of Health and the Alcohol, Drug Abuse and Mental Health Administration.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1987	$106,733,000	$140,225,000	$129,475,000	$138,713,000
1988	123,009,000	---	---	---
1988	132,089,000	154,632,000	153,867,000	147,679,000
1989	158,244,000 2/	155,487,000 2/	161,244,000 2/	159,897,000 3/
1990	167,334,000 4/	171,673,000	171,688,000	171,250,000 5/
1990 Sequester				-2,320,000
1991	176,080,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Excludes funds for AIDS research and education ($687,000).

3/ Excludes funds for AIDS research and education ($673,000), for Gramm-Rudman-Hollings spending targets ($1,943,000), and for the FY 1989 Procurement Reform Reduction ($91,000).

4/ The 1990 request excludes funds for the National HIV program ($1,254,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

5/ Excludes enacted administrative reductions of $431,000.

Justification

National Institute of Arthritis and Musculoskeletal and Skin Diseases

	1990 Appropriation		1991 Estimate		Increase or Decrease	
	FTE	BA	FTE	BA	FTE	BA
TOTAL....	116	$168,927,000	122	$176,080,000	+6	$7,153,000
HIV/AIDS..	(3)	(1,238,000)	(4)	(1,483,000)	+1	(+245,000)

General Statement

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) stimulates and supports research on a broad range of diseases and long-lasting, disabling conditions in the fields of rheumatology, orthopaedics, bone and mineral metabolism, muscle biology and dermatology. The Institute supports research projects and programs, research training and manpower development, collects data on the incidence and prevalence of the diseases that are under study, and disseminates research findings to health professionals and the general public.

More than 37 million Americans--1 in 7--have some form of arthritis or other rheumatic disease. Approximately one-third of all adults are affected by joint swelling, limitation of motion, or pain. More than 80 percent of persons older than 75 have evidence of osteoarthritis. An estimated 200,000 children have some form of arthritis, and some of them will carry a serious handicap into adulthood.

The economic cost of arthritis and rheumatic disease is staggering. Direct costs of medical care and indirect costs, such as those due to lost wages, amount to $35 billion per year. In that a large percentage of those with arthritis are 65 years of age and older, an investment in research to diminish disease and disability will alleviate the economic burden from these disorders on the Nation and improve the quality of life for patients.

Osteoporosis is the leading cause of bone fracture in the elderly, particularly in women. Rapid bone loss begins at menopause. The prevalence of osteoporosis increases with age; 90 percent of women 75 years of age and older have moderate or severe osteoporosis. The lifetime risk of hip fractures in white women is as great as the risk of breast, endometrial, and ovarian cancers combined. Twenty percent of all hip fractures contribute to death within one year after fracture.

Musculoskeletal trauma is a serious health problem in the nation. Noteworthy are the increasing injuries resulting from fitness activities by non-athletes, as well as athletes. Many of the survivors from accidents

become permanently disabled by traumatic arthritis, fracture deformities, or chronic bone infection.

Impairments of the back and spine are the leading cause of limitation of activity among young persons 17 to 45 years of age. Back pain affects 80 percent of Americans at some time in their lives. More than 15 percent of applications for Social Security disability are for musculoskeletal impairment; of these back problems account for half of the direct medical costs and for three-quarters of the indirect costs.

As many as 60 million Americans have one or more skin diseases that require a visit to a physician at least once a year. These diseases cause physical and psychological suffering, especially when disfigurement is severe. Epidermolysis bullosa is one of the most disabling of the skin diseases. Psoriasis affects people of all ages, with an estimated 2 to 3 million cases in the United States.

The arthritis research program is concerned with more than 100 forms of rheumatic disease, including rheumatoid arthritis, osteoarthritis, Lyme disease, systemic lupus erythematosus, scleroderma, Sjogren's syndrome, the spondyloarthropathies, and gout. The orthopaedic and bone biology programs include studies of normal bone, bone growth and bone metabolism; bone diseases, such as osteoporosis; joint diseases; bone and joint injury and repair; and therapies such as joint replacement and cartilage transplantation. Research on muscle biology provides the foundation for understanding how muscle develops and functions normally, and how it malfunctions in disease. Investigations of skin disorders are under way on a wide range of problems, including blistering diseases, such as pemphigus and epidermolysis bullosa; keratinizing disorders, such as psoriasis and ichthyosis; atopic and contact dermatitis; and other chronic inflammatory skin diseases.

The Intramural Research Program consists of two principal entities. The Arthritis and Rheumatism Branch is carrying out research efforts on: the immunologic bases of diseases such as systemic lupus erythematosus; the action of antibodies and their receptors; the pathophysiology and potential therapies for rheumatoid arthritis and polymyositis; and normal bone growth and development and regeneration of bone after trauma. The Laboratory of Physical Biology conducts research on how muscles generate force, how alterations in fundamental muscle structure play a role in diseases such as muscular dystrophy, and how proteins fold to make muscles contract.

Overall Budget Policy

The overall budget request for NIAMS totals $176,080,000, an increase of $7,153,000 over the comparable 1990 level of $168,927,000. Included in the request is provision for AIDS research at $1,483,000, an increase of $245,000 over the 1990 amount.

At the 1991 request level, the Institute will support 494 noncompeting research project grants at $87,610,000 and 150 competing grants at $30,377,000 compared to 508 and 135, respectively, in 1990.

Research centers will remain at the 1990 level: 26 centers at $21,025,000.

The 1991 request includes a decrease of $85,000 and one award for research career awards from the 1990 level. Minority biomedical research support includes an increase of $29,000 over 1990.

Approximately 225 full-time training positions at a cost of $6,742,000 will be supported within the 1991 request for research training--the same as the 1990 level.

A total of $3,692,000 will be available for research and development contracts, compared to $3,702,000 in 1990.

Intramural research will be conducted at a level of $12,922,000 and 61 FTEs, compared with $12,077,000 and 57 FTEs in 1990.

Research management and support activities will be funded at $7,643,000 and 61 FTEs, compared to $6,724,000 and 59 FTEs in 1990.

Program Accomplishments

Lyme Disease. Lyme disease is a growing problem in the nation. It affects many parts of the body; primarily the skin, joints, heart, and brain. It is caused by a bacterium, Borrelia burgdorferi, that is transmitted by ticks. Some 5,000 new cases were reported in the United States last year, and the incidence is increasing. Because the symptoms of Lyme disease mimic those of other ailments, it is often difficult to make an early specific diagnosis. Researchers have recently developed a test for detecting Lyme disease bacteria in urine; the test uses highly specific antibodies. This new test may prove to be more accurate and faster than the diagnostic blood tests in current use.

When Lyme disease was first reported as a new form of arthritis to the Connecticut State Health Department in 1975, it was thought to be a new clinical entity. Since then, scientists have learned that a similar disease has been present in Europe since the beginning of the 20th century, and occurs in many other parts of the world. Findings from a cooperative study conducted by American and Soviet researchers has shown that Lyme disease exists in different regions of the U.S.S.R., and there seem to be different strains of the causative bacterium in the different regions. This may explain the regional differences in the expression of Lyme disease throughout the world.

Rheumatoid Arthritis. Approximately 2.1 million adults in the United States suffer from rheumatoid arthritis; more than two-thirds are women. Although the disease can start at any age, it usually begins in mid-life. The symptoms include inflammation of joints with acute pain, fatigue, weight loss, sleep disturbances, and malaise.

Definitive therapeutic trials have established the efficacy of some treatments, such as methotrexate, allowing prompt approval by the Food and Drug Administration.

Using an animal model with many features of human rheumatoid arthritis, investigators showed that a powerful enzyme inhibitor is effective in suppressing an erosive arthritis. The inhibitor strikingly reduced the degree of joint inflammation, thus supporting the concept that such enzyme inhibitors may be useful in treating similar arthritic conditions in humans.

Infectious Etiology. Several infectious agents are potential causes of one or another form of arthritis. Using new experimental genetic techniques, researchers were recently able to show that mice carrying a specific genetic trait closely associated with human spinal arthritis are more likely to die following bacterial infection than are normal animals. These transgenic mice are now available for investigating the roles of both infectious agents and the immune system in the causation of arthritis.

Systemic Lupus Erythematosus. Systemic lupus erythematosus (SLE) is an inflammatory immune-mediated disorder, largely of young women, that causes distinctive rashes, arthritis, and kidney damage. Lupus is an "autoimmune" disease, in which the body produces antibodies that react against one's own tissues. It is much more frequent in women than in men (9-1). Lupus is also three times more common in black than in white women.

Using modern, sophisticated laboratory procedures, researchers have shown that certain autoantibodies, anti-Ro, are present in about half of lupus patients. Detailed genetic studies of families of lupus patients indicate that the tendency to develop these antibodies is under close genetic control. This provides a better understanding of the unequal racial distribution of this disease and the reasons why some persons become affected and others do not. The "autoimmune trait" showed a 92 percent penetrance in female relatives of lupus patients.

Lupus can also be induced by certain drugs. Drug-induced lupus is characterized by a strong immune response to the genetic material, DNA, contained in the cell nucleus. Investigators have recently found that two lupus-inducing drugs could bring about structural changes in DNA that might render it susceptible to attack by the immune system.

Osteoporosis. Osteoporosis is a condition in which the density and strength of bone is reduced to such an extent that fractures result. At present, there is no proven successful treatment for osteoporosis. Sodium fluoride was believed to be a promising candidate in that it can increase bone mass in the spine; however, the quality of the new bone has been questionable. Recently, a major long-term clinical trial, supported by NIAMS, to determine if fluoride therapy is effective in reducing the incidence of vertebral fractures was completed. Fluoride was found not to be effective in this regard.

Progress has been made in understanding why the prevalence of osteoporosis in Black persons is lower than in white persons. The metabolism (turnover) of bone was found to be less in blacks as compared to whites. Unraveling the details of this metabolic phenomenon may lead to a new conceptual approach to the prevention or treatment of osteoporosis.

Inadequate calcium intake can be a contributing factor in the bone loss of postmenopausal women and the elderly; men and women at risk for bone loss are advised to increase their calcium intake. However, the amount of calcium available from various natural food sources and an understanding of the calcium absorption has not been clear. Researchers are investigating how calcium is absorbed from a variety of food sources. Calcium from tablet supplements have been found to be better absorbed if taken with a meal.

Bone mass is regulated by a complex interaction of genetic factors, nutrition, mechanical stress, and endocrine status. An important thrust of current research is to identify those changes in lifestyle, such as exercise and nutrition, that can increase the adult peak bone mass (the maximum bone mass achieved by age 35), before bone loss begins thereafter. Investigators have recently shown that women 25 to 34 years of age who are physically active have significantly higher spinal bone mass than have women of the same age who are physically inactive. Low spinal bone mass is a major factor in determining the likelihood of spinal compression fractures. This research indicates that regular exercise and an adequate calcium intake throughout life may significantly delay the onset of osteoporotic fractures.

The vertebrae of the spine consist of mostly sponge-like, trabecular bone surrounded by a shell of dense cortical bone. While bone density is highly correlated with bone strength, it has also become increasingly clear that specific architectural changes in trabecular bone are important in determining the resistance of bone to fracture. Investigators have demonstrated that in osteoporosis, there is a loss of horizontal cross-bracing struts of bone, leaving thin vertical columns of bone that are weak and likely to fracture.

Bone Biology. A new protein, osteopontin, has been discovered that plays a role in attachment of bone forming cells to its local substrate. It may provide the scaffold onto which bone forming cells attach and spread. In other studies, since bone clearly responds to its mechanical environment, as demonstrated by the loss of bone in the weightlessness of space, research is active on uncovering the response of bone cells to mechanical loading.

Muscle Biology. Skeletal muscle constitutes more than 50 percent of the weight of the human body. It is responsible for all movement and does so by generating energy. Molecules within muscles must twist and fold to produce the contraction of muscle. Researchers are continuing to investigate thoroughly the chemistry and anatomy of molecules that contract.

Osteoarthritis. Osteoarthritis, the most common form of arthritis, is the result of degeneration of cartilage and other joint structures. The primary cause is unknown. Investigators have recently used a new microscopic computerized X-ray technique to detect the sequence of events leading to osteoarthritis. They have reported that the earliest changes occurred, not in the cartilage as previously thought, but rather in the bone that lies just beneath the cartilage. Other researchers have identified a protein that is found in the cartilage from osteoarthritis patients, but not in cartilage from normal adults.

Bone Cell Response To Mechanical Stress. Bone adapts to an increased load by altering its growth process in a way that resists increased stress. Recent development of a tissue culture model has allowed the further investigation of this important process. Isolated bone cells are placed on a flexible culture dish and subjected to a controlled mechanical strain. Bone cells were found to increase their rate of division and to align in response to mechanical tension.

Collagen Gene Defects in Osteogenesis Imperfecta. Osteogenesis imperfecta (OI), or "brittle bone disease", is one of the major heritable disorders of connective tissue. One or more defects of collagen genes have been discovered in OI; they are thought to play a critical role in the pathogenesis of OI. Investigators have recently used the polymerase chain reaction to characterize a specific DNA defect expressed in the fibroblasts (cells) of patients with OI. This DNA defect alters the assembly of the collagen and leads to defects observed in the connective tissues of these patients.

Epidermolysis Bullosa. Epidermolysis bullosa (EB) is a group of devastating blistering diseases. The National Epidermolysis Bullosa Registry established by the NIAMS functions both to collect patient data and material and to assist researchers investigating EB. Researchers utilizing this

registry identified a number of genetic markers on the surfaces of cells from patients with recessive dystrophic EB--one of the most severe forms of the disease. Preliminary findings indicate that there may be a linkage between a specific chemical defect in this type of EB and the genetic markers.

Alopecia. Alopecia is a group of disorders resulting in hair loss. The psychological impact can be debilitating. Minoxidil, a drug that was originally developed for treating high blood pressure, has been shown, under certain conditions to facilitate hair growth, but its mechanism of action has not been firmly established. Studies indicated that minoxidil initiates and maintains the active-growth phase of the life cycle of hair uninterrupted by normal resting periods. This observation provides additional information concerning the control of the normal life cycle of hair and could lead to development of better therapies to prevent hair loss.

Sunlight and Skin. Exposure to ultraviolet (UV) light in an amount sufficient to induce sunburn has been shown to have immunologic effects both locally in the skin and systemically. In animal models, exposure of the skin to an amount of UV light that does not produce redness leads to suppression of contact hypersensitivity, the skin's reaction to contact with allergic chemical substances.

Intramural Research

Basic Immunology. In an advance that may bring a new era in the treatment of allergies, NIAMS intramural scientists have determined the complete structure of a key protein--called the IgE receptor--involved in triggering allergic reactions. When allergy-producing substances, such as ragweed pollen and cat dander, attach to the surface of cells lining airway passages, these cells spill out powerful chemicals that produce sneezing, itching, and inflammation. The discovery of the IgE receptor structure allows scientists to search for a new class of drugs that will prevent allergy attacks by specifically blocking the binding of antibodies to IgE receptors.

Knowledge of the structure and function of the IgE receptor provides a new opportunity to study the binding of other antibodies that occur in several other immune-mediated diseases, such as lupus, Sjogren's syndrome, rheumatoid arthritis, and pemphigus.

Neuroendocrine Control of Arthritis. Researchers have been able to provide biologic evidence of a defect in the neuroendocrine response to inflammation in an animal model of persistent arthritis. Certain selected strains of rats develop arthritis in response to injection of bacterial components; most strains do not. It has been shown that those animals that developed arthritis had a defect in their neuroendocrine system. In very recent work, normal rats developed arthritis after treatment with a drug that blocks the effects of naturally occurring brain-controlled anti-inflammatory hormones. The mechanisms elucidated in these studies could prove to be helpful in understanding the causal factors in human autoimmune diseases, especially rheumatoid arthritis.

Treatment of Lupus Nephritis. Intramural scientists have had a long-standing interest in treating patients with lupus nephritis, one of the most

serious complications of systemic lupus erythematosus. Without treatment some patients' only hope for survival is kidney dialysis or transplant. The Intramural Research Program currently has a 20-year follow-up of a patient population that is unparalleled anywhere in the world. Our NIH scientists have recently completed a follow-up study of patients randomized to one of three different drug treatments. These data indicate that, in the long term follow-up, the group of patients given intravenous cyclophosphamide, a drug normally used to treat cancer, developed much less kidney failure than did the other two groups. In that kidney failure is usually a late development, previous short term studies had failed to show this improvement.

Duchenne Muscular Dystrophy. Duchenne muscular dystrophy (DMD) is a devastating, ultimately fatal genetic disease occurring once in every 3,500 live male births. Children typically develop muscle weakness around age six, followed by increasing motor difficulty. Using techniques originally developed to study single muscle fibers in animals, NIAMS intramural scientists recently examined the muscle fibers of patients with DMD. They found that individual fibers functioned normally, suggesting that the clinical weakness in the muscular dystrophy may be due to a deficiency in the number of muscle fibers rather than to a defect in the fiber itself.

Cryo-Electron Microscopy. During the past year, facilities for performing cryo-electron microscopic studies were installed and tested in the Institute's intramural laboratories. This instrument is capable of showing the structure of biological specimens as they exist in life undistorted by artifacts. Scientists are now using the new instrument to determine the structure of viruses, such as HIV; how lipids are incorporated into cell membranes; and how substances of widely different sizes can be carried across these membranes.

AIDS Research Program

The NIAMS AIDS Programs

The NIAMS AIDS research program supports and conducts research on the skin, rheumatic and musculoskeletal manifestations of human immunodeficiency virus (HIV) infection.

Recent Research Accomplishments

Human immunodeficiency virus infection is associated with a variety of skin diseases--psoriasis, folliculitis, seborrheic dermatitis, molluscum contagiosum, and Kaposi's sarcoma. Psoriasis, a chronic skin disease characterized by a scaly rash, is more severe, and may be more prevalent, in AIDS patients than in the general population. Researchers supported by NIAMS have shown that psoriasis regresses in HIV-infected individuals treated with zidovudine (AZT). The psoriasis worsened after reducing or discontinuing the medication, and then disappeared after treatment with AZT was resumed, despite evidence for progression of the HIV infection itself. By studying individuals with psoriasis and AIDS, researchers can further understand the cause of psoriasis and its relation to the immune system.

Researchers have recently found that the HIV virus can be transmitted in skin grafts used to cover wounds in severely burned patients. NIAMS-supported investigators, by utilizing the polymerase chain reaction, a new technology, have been able to detect minute quantities of HIV infection in skin biopsy tissue. This procedure for detecting HIV infection will make skin grafting a safer procedure.

Research Plans

A collaboration between the NIAMS and the U.S. Army to study the various skin manifestations of HIV infection has been established. Army personnel infected with HIV are being evaluated at the Walter Reed Army Medical Center, Washington, D.C. This comprehensive study, to be conducted over a ten-year period, will include research on drug reactions, infectious complications, the effects of HIV infection on the normal bacterial population of the skin, and the extent to which the skin harbors potentially harmful organisms in various stages of HIV infection. These investigations are designed to: discover early skin manifestations of HIV infection that may be predictors of the patient's future clinical course of AIDS or its prognosis; document the cutaneous manifestations of HIV-related drug rashes and address the mechanisms by which they occur; and further the understanding of those skin disorders such as seborrheic dermatitis, occurring in otherwise healthy individuals, that are even more common and severe in HIV-infected individuals.

HIV infection also appears to be associated with certain rheumatic and musculoskeletal diseases and manifestations. Reiter's syndrome, a disorder of young men and women assumed to have an infectious etiology and characterized by inflammation of the joints, spine, eyes, mouth, and urethra has been reported to develop more frequently and severely in patients infected with HIV than in the general population. Further

research will address the nature, cause and treatment of Reiter's syndrome in AIDS patients.

NIAMS researchers are working closely also with rheumatologists at the Walter Reed Army Medical Center to establish protocols to study the rheumatic and musculoskeletal manifestations of HIV infection in Army personnel. The military population presents a unique opportunity for prospective studies begun at the earliest stage of HIV infection. Plans are being made to establish a repository of blood samples from these patients for future investigations. These collaborative studies will enhance our understanding of how the interaction of immunosuppressive and infectious processes produce rheumatic disease in HIV-infected individuals and are likely to improve treatment of rheumatic disorders occurring both in AIDS patients and individuals without HIV infection in the general population.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Arthritis and Musculoskeletal and Skin Diseases

Authorization: Indefinite.

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$149,762,000	$155,515,000	+$5,753,000

Purpose and Method of Operation

The Arthritis and Musculoskeletal and Skin Diseases Program is responsible for stimulating and supporting a broad range of basic and clinical research on many of the most debilitating diseases affecting the health of the Nation. This research encompasses the many forms of arthritis, diseases of the musculoskeletal system and skin, as well as studies of the normal structure and function of joints, muscles, bones, and skin. The disciplines involved include immunology, molecular biology, genetics, virology, pharmacology, and biochemistry. Multidisciplinary approaches to basic problems have proven especially valuable in fostering increased research productivity.

Many mechanisms are employed to foster investigator-initiated research, including research project grants, program project grants for more broadly based multidisciplinary research, and research career awards. Through the Research Career Program, the Institute promotes and supports career development of both basic and clinical researchers utilizing Research Career Development Awards, Clinical Investigator Awards, and Physician Scientist Awards.

Highly competitive, successful Multipurpose Centers in Arthritis and Musculoskeletal Diseases are also supported by the Program. Each Center has components concerned with basic and/or clinical research and educational and health services research. The Specialized Centers of Research (SCORs) support multidisciplinary research with both a basic science and a clinical research emphasis in three diseases of national importance: rheumatoid arthritis, osteoarthritis, and osteoporosis. The Institute also has a core centers program in dermatology.

The Institute supports both Individual and Institutional National Research Awards for both predoctoral and postdoctoral research training to ensure a sufficient number of trained research scientists.

The contract mechanism is used by the Institute to obtain specific research as determined by program needs. This mechanism has been used for several years to support clinical trials on various drug therapies for rheumatic diseases. The National Patient Registry on Epidermolysis Bullosa is also supported by the contract mechanism.

Arthritis and Related Diseases

Rheumatoid Arthritis. Rheumatoid arthritis causes pain and inflammation in many of the body's joints. Joint cartilage, tendons, bones, and other surrounding structures can be severely damaged. Treatment has improved in recent years, but much remains to be learned. Additional work will focus on the chemical and cellular basis of the immune response, on mediators of inflammation, and on enzymes that participate in joint destruction.

Genetic and immunologic processes have been implicated in the initiation and perpetuation of rheumatoid arthritis. A recent workshop brought together basic scientists studying chemical and cellular components of the immune system and clinical investigators studying the association of human leucocyte (HLA) antigens, genetically determined cell markers, and susceptibility to rheumatoid arthritis and certain other rheumatic diseases. This interaction lead to the establishment of recommendations for future research and collaboration.

Immunogenetic studies suggest that different HLA antigens share identical stretches of amino acids, and it may be these shared "epitopes" that predispose a person to disease. Computer searches have identified amino acid sequences that are shared between certain microbial organisms and HLA epitopes. This homology may be important in the development of rheumatic disease.

Later this year, the Institute will begin a clinical trial of minocycline (a form of tetracycline) for the treatment of rheumatoid arthritis. Investigators have observed that minocycline inhibits the activity of collagenase--an enzyme that breaks down collagen, the major protein of cartilage and other structures of joints. The clinical trial is based on the hypothesis that inhibiting collagenase activity in the joints of patients with rheumatoid arthritis will prove beneficial. If minocycline is effective, the next step would be development and evaluation of a form of tetracycline that retains the collagenase inhibiting properties of minocycline, but not its antibiotic properties.

Lyme Disease. Lyme disease is a tick borne disease with a wide range of symptoms, including a characteristic skin rash, arthritis, neurologic and cardiac manifestations. Oral antibiotics, such as penicillin, erythromycin and tetracycline, usually shorten the duration of early symptoms, and they appear to prevent progression of the disease in many patients. Future clinical studies will define optimal treatment regimens for the various stages of the disease. In particular, improved treatments for the later, more serious arthritic and neurologic complications of Lyme disease need to be developed.

At present, it is not clear whether tissue damage in Lyme disease is caused directly by the bacterium or mediated by the body's immune system. In conjunction with the National Institute of Allergy and Infectious Diseases, the NIAMS will focus future efforts on further understanding the interactions between the bacterium (Borrelia burgdorferi) and the immune system. Increased knowledge in this area will lead to substantial improvements both in diagnosis and chemotherapy, and may provide the basis for the development of an effective vaccine.

Epidemiologic studies will determine the prevalence and incidence of Lyme disease, whether or not Lyme disease is spreading, and whether the disease varies geographically. Some people appear to be particularly susceptible to developing the late manifestations of Lyme disease; efforts will be made to define the risk factors in such individuals.

Systemic Lupus Erythematosus. Lupus, a serious disease of young women, is an inflammatory, immune-mediated disease that affects many different organs of the body. Over the past several decades there has been impressive improvement in the treatment of lupus--attributable to many factors, including the ability of new immunosuppressive agents to blunt the disease process. However, these treatments are toxic and not uniformly effective. Moreover, both the underlying cause and prevention of lupus remain unknown.

Several important questions need to be further addressed: how many types of lupus are there and how common is each; why is lupus more common in women than men; why is it more common in black than in white women; and does lupus run in families? Continuing research on the epidemiology of lupus will yield a clearer understanding of the numbers and types of people affected by the disease. Research is also being pursued to identify initiating factors that trigger the immunologic defects in lupus. The Institute will sponsor an international workshop in 1991 to assess current knowledge of lupus and suggest additional research directions.

Pediatric Rheumatic Diseases. Childhood rheumatic diseases include a large number of illnesses affecting both joints and related structures. Juvenile arthritis is the most frequent of the pediatric connective tissue diseases and a leading cause of disability. Juvenile arthritis has been found to be associated with specific genetic types that convey susceptibility to disease. The Institute will encourage research approaches and opportunities that are particularly relevant to children--for example, their hormonal environment, types of infections, and an immune system that differs from that of adults.

Sjogren's Syndrome. Sjogren's syndrome is a chronic inflammatory disease resulting in dry mouth, dry eyes, and a variety of other manifestations. Connective tissue diseases, such as systemic lupus erythematosus and rheumatoid arthritis, are often associated with Sjogren's syndrome. Research on the disease has focused on interrelationships between autoimmunity and lymphomas, which occur in patients with this complex syndrome. Following a January 1989 conference discussing current knowledge

of the diagnosis and treatment of Sjogren's syndrome, investigators met to identify needs and opportunities for research. Future research will be directed toward standardization of diagnostic criteria, epidemiologic studies, and the possible role of viruses and genetic factors in the causation of the disease. An animal model for Sjogren's syndrome was recently developed, and may provide further insights into autoimmune mechanisms that relate to Sjogren's syndrome.

Scleroderma. Systemic sclerosis (scleroderma) is a disease that affects the skin and internal organs. The typical first complaint of patients with scleroderma is either Raynaud's phenomenon (blanching of fingers and toes due to spasms of small blood vessels on exposure to cold) or diffuse swelling of the hands. Although the hallmark of scleroderma is taut skin, this does not develop until later in the disease. Several new drugs are effective in treating certain manifestations of scleroderma. However, no single agent has proved capable of altering the underlying, natural course of scleroderma. Recent studies have identified several abnormalities in scleroderma that may be susceptible to intervention. The Institute will stimulate research that will enhance knowledge of the small blood vessel pathology, immunologic events, and connective tissue overgrowth, that are features of scleroderma.

Spondyloarthropathies. Spondyloarthropathies are inflammatory diseases that affect the spine. Among them are ankylosing spondylitis and Reiter's syndrome. The Institute will focus research efforts on discovering the reasons for the predilection of these diseases for young men and women, and how genetic factors and antecedent bacterial infections appear to predispose individuals to these disorders. To explore further such factors in these disorders, the NIAMS, in collaboration with the Indian Health Service, is conducting an epidemiologic study of ankylosing spondylitis in Eskimo populations. This population seems to have an unusually high frequency of both spondylitis (spinal arthritis) and a genetic marker associated with ankylosing spondylitis. Moreover, as part of the U.S.-U.S.S.R. bilateral agreement in arthritis, this study will also compare Siberian and Alaskan Eskimo populations to elucidate the roles of genetic factors and environmental triggers of this disease.

Immunogenetics. A scientific workshop sponsored by NIAMS on the immunogenetics of the rheumatic diseases provided recommendations for future research directions focusing on correlations between genetically determined markers in blood that seem to convey susceptibility to rheumatoid arthritis and other rheumatic diseases. The workshop highlighted the need to expand the search for microbial and environmental agents that may "trigger" rheumatic disease in a susceptible person, and the importance of developing additional animal models of arthritis and related diseases.

Musculoskeletal Diseases

Osteoporosis. There are two major forms of osteoporosis: type I related to menopause, and type II related to increasing age. Estrogen replacement has been developed as an effective method to reduce the bone loss in type I osteoporosis, but there is no universally effective method of prevention or treatment for type II osteoporosis. The NIAMS and the National

Institute on Aging have issued jointly a program announcement to encourage additional research to determine whether these two syndromes have different etiologic mechanisms and to develop theories of pathogenesis that will lead to the prediction, prevention, and treatment of type II osteoporosis. Basic research studies will be directed at the role of age-related changes in bone biochemistry, bone turnover, hormone function, and mineral absorption.

There are few reliable data on the different frequencies of osteoporosis and related fractures in different countries and various ethnic groups around the world. NIAMS is collaborating with the World Health Organization and the National Institute on Aging to conduct a major epidemiologic study to determine if the rates of osteoporosis and fractures vary. Differences between groups may discover specific genetic or environmental risk factors, and in this way, suggest new approaches to prevention and treatment of osteoporosis. The study complements the ongoing Third National Health and Nutrition Examination Survey conducted by the National Center for Health Statistics.

A scientific workshop, "Research Advances in Osteoporosis," will be held on February 26-28, 1990. Participants will review the latest information from basic and clinical research, help physicians choose the best current methods for measuring bone mass and bone quality, and set the stage for continued research in this important area.

Low Back Pain. Low back pain affects most Americans at some time in their life, and its enormous impact on the Nation's health is well documented. Both the causes and optimal treatment of low back pain are uncertain. The NIAMS and the American Academy of Orthopaedic Surgeons jointly sponsored a multidisciplinary workshop to review basic and clinical studies on the relationship between low back pain and the nervous system, back muscles, intervertebral disc, and skeletal support structures. The workshop thoroughly assessed recent progress and developed directions for future studies. The workshop was published in February 1989 in book form as New Perspectives in Low Back Pain.

Workshop participants identified the need for investigations to assess conditions that make certain back muscles more susceptible to injury, and more research to determine how back muscles respond to spasm. Research on exercise as treatment and the role of muscle strengthening in the prevention of low back pain are needed. Further research on skeletal support structures should include studies on the effects of inactivity and exercise on ligaments, facet joints, and other supporting structures; and research on the anatomical, mechanical, and biochemical functions of spinal ligaments and their relationship to the aging/degeneration process. In many areas of low back research, collaborative efforts among several scientific disciplines are required.

Musculoskeletal Fitness/Sports Medicine. Guidance to reduce risk of injury is important for the millions of Americans participating in exercise programs and sports. The NIAMS, both through scientific workshops and a research program announcement, has encouraged increased research in these areas. In the Spring of 1989 a workshop was held on inflammation generated

by sports-induced tissue injury. A book summarizing this workshop and containing the current scientific knowledge base and directions for future research directions will be published shortly. A program announcement based on the recommendations from this workshop will be issued to encourage further research in this important field.

Osteoarthritis. Further research will focus on elucidating the causes of osteoarthritis and developing new treatments. Several investigators are studying the interaction between porous-coated joint replacements and the surrounding bone tissue. The ingrowth of natural bone into the pores can potentially enhance both the stability and the longevity of the joint replacements. A recent workshop focused on biological restoration of joint surfaces using graft materials.

Heritable Connective Tissue Disorders. Inherited disorders of connective tissue can have a devastating impact on the many individuals suffering from them. These disorders include osteogenesis imperfecta, Ehlers-Danlos syndrome, and Marfan's syndrome. Investigators are using the tools of modern molecular biology to gain a better understanding of how basic genetic defects lead to the specific clinical symptoms and features of each disease. The Institute is sponsoring and convening a Scientific Workshop in April, 1990 to bring together the leaders in this field and set future research directions.

Paget's Disease of Bone. Treatment of bone diseases requires a thorough understanding of the complex process of bone remodeling: a continuing process of bone resorption and bone rebuilding. In certain bone diseases, an imbalance in bone remodeling may produce structurally unsound bone. Paget's disease of bone is such a chronic disease characterized by abnormally high bone turnover resulting in bone that is dense but fragile. It often leads to striking bone deformities, such as an enlarged skull or bowing of the legs. The NIAMS has issued a program announcement to stimulate both basic and clinical research to further our understanding of Paget's disease. Research will target the possible role of viruses in pathogenesis, examine local and systemic factors involved in control of bone remodelling, and attempt to determine is there is a genetic susceptibility in this disorder.

Muscle Biology. Muscle membranes contain channels that regulate the flow of ions and metabolites in and out of tissue. The level of muscle activity is controlled by a delicate balance of channels, especially those that pump calcium into and out of cells. It has been possible to purify and make clones of the proteins composing the calcium channel and, using these, to identify very small mutations that make large differences in a person's health. One such mutation is probably responsible for a potentially lethal complication of anesthesia, known as malignant hyperthermia. The ability of investigators to purify and reproduce the protein may give clues to eventual therapy.

The relationship of chemical structure of muscle protein to muscle function is poorly understood. NIAMS will sponsor a workshop on molecular genetics and genetic engineering in muscle to analyze in detail the current

state of knowledge of the structures and functions of the molecules that make up muscle, and to study and stimulate research in this area.

Skin Diseases

Epidermolysis Bullosa. Research into the cause, pathogenic mechanisms, and potential treatments for the disabling group of blistering diseases known as epidermolysis bullosa (EB) has been hampered by lack of an animal model. Recently, however, scientists have discovered that certain inbred sheep manifest the characteristics of recessive dystrophic EB, one of the most severe forms. The presence of such an animal model of this human disease opens new avenues of research, including the ability to conduct drug intervention studies more easily.

Recessive dystrophic epidermolysis bullosa is one of the genetic forms of EB. In recessive dystrophic EB, the microscopic fibers that link the outer layer of the skin to the inner layer are absent, and researchers believe that an abnormal enzyme may be responsible. Because laboratory evidence indicates that phenytoin, an anticonvulsant, decreases the activity of the abnormal enzyme, the drug has been used in the treatment of recessive dystrophic EB. However, a recent clinical trial demonstrated the drug to be ineffective. The patient population now being recruited by the EB Registry will facilitate future clinical trials so that other candidate drugs can be tested. In addition, the registry will identify populations that can be used to differentiate the various forms of EB and delineate the abnormal pathology more precisely.

Sunlight and Skin. An NIH Consensus Development Conference on Sunlight, Ultraviolet Radiation, and the Skin was held in May 1989, sponsored by the NIAMS and the Office of Medical Applications of Research, and cosponsored by other NIH institutes and Federal agencies. Many recommendations related to human exposure to natural and artificial ultraviolet (UV) light emerged from the conference. Efforts will focus on implementing a program of prevention that will effect a reduction to ultraviolet exposure in susceptible populations.

The Consensus Development Conference panel also identified areas needing further research. Among these were the effects of UV on the skin and the biology of aging skin. Many people purposely expose their skin to additional ultraviolet light, either from sunlight or artificial sources. Although some of the adverse effects are known, the specific mechanisms involved are not well understood. Only recently has it been recognized that UV modifies immune function, both locally and systemically. Research will continue to study the immune dysfunction of skin, resulting from both acute and chronic UV exposure. The Institute will encourage research related to the biology of aging skin, because there is confusion about intrinsic aging versus photoaging and controversy about the ability of certain topically applied drugs to remove wrinkles.

Alopecia. The NIAMS assembled a scientific advisory group that recommended further studies on the basic biology of hair and its diseases--

with special reference to understanding the hair cycle, control mechanisms, and possible clinical applications. Recent improvements in culture techniques, particularly the development of an organ culture system to study hair growth, and the development of new animal systems to test certain drug treatments for hair loss make this a particularly timely and promising opportunity.

Psoriasis. Psoriasis is one of the most prevalent and disabling of skin diseases. The underlying pathogenesis of the disease remains unknown. In September 1989, a NIAMS-supported workshop on psoriasis recommended substantial additional research on the molecular, immunologic, and pharmacologic aspects of the disease.

Wound Healing. Healing of skin wounds, both from traumatic injury and as part of surgical procedures, is of great medical interest; it also has a major impact on health care costs in the United States. During the last several years, knowledge concerning interventions that seem to speed wound healing has been enhanced greatly by the development of "second skin" dressings. These are of several types; and have been shown to be useful in many diverse clinical situations. The basic processes by which they improve wound healing, however, are not well understood. Research efforts will focus on both molecular mechanisms and clinical aspects of wound healing.

Health Interview Survey. Arthritis and musculoskeletal and skin diseases affect both sexes and all ages and races, but with much variation among subgroups. The NIAMS, in collaboration with the National Center for Health Statistics, is developing a new set of questions on these diseases for the National Health Interview Survey (NHIS). Data from the NHIS will be used for health care planning and development of strategies for intervention in groups identified to be at high risk for these diseases. These data will also be used to evaluate the Year 2000 National Health Objectives, a DHHS initiative that formulated national objectives for disease prevention and health promotion for the year 2000.

Rationale for the Budget Request

The FY 1991 request of $155,515,000 represents an increase of $5,753,000 over the comparable 1990 estimate. Research project grants increase $5,819,000. The same number of centers, research training, and research and development contracts will be funded as in 1990.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Intramural Research Program

Authorization: Indefinite.

Budget Authority:

1990 Appropriation		1991 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA
57	$12,077,000	61	$12,922,000	+4	+$845,000

Purpose and Method of Operation

The Institute's intramural research activities range broadly from studies on patients at the NIH Clinical Center for improving treatments for rheumatic diseases to ultrastructural analysis of folding of muscle protein. Two major units have carried out this research: the Arthritis and Rheumatism Branch and the Laboratory of Physical Biology. A new unit, the Laboratory of Skin Biology was recently created.

Scientists in the Arthritis and Rheumatism Branch conduct fundamental studies on mechanisms of immune responses and clinical and laboratory research on systemic lupus erythematosus, rheumatoid arthritis, and polymyositis, and research on bone metabolism and its repair. Research in the this branch is multidisciplinary--involving biochemistry, molecular biology, genetics, cell biology, immunology, pathology, pharmacology, and clinical investigations.

In the Laboratory of Physical Biology, investigators study fundamental biological problems in muscle contraction and lipid biophysics, as well as the structure and assembly of filaments, membranes, and other complex molecules that compose muscle, skin, and bone. In addition to collaborations between NIAMS intramural scientists, there are many cooperative projects with other scientists at the NIH, across the United States, and abroad.

The NIAMS Intramural Program provides training for physicians who wish to pursue careers as independent clinical investigators. Currently, a total of seven individuals participate in this program. To foster more research on arthritis in children, the Institute initiated a Pediatric Rheumatology Research Program in 1989. Under a collaborative agreement with Children's Hospital National Medical Center, a 3-year program for one new trainee per year has been established. The first fellow was enrolled July 1, 1989.

Rheumatoid Arthritis. A fundamental characteristic of human rheumatoid arthritis is proliferation of cells. In collaboration with researchers in the National Cancer Institute, NIAMS scientists are investigating the role of two important growth factors in regulating this proliferation. They are

investigating abnormal cells in inflamed joints, how their activity is controlled, and the role that other body components play in development of the diseased joint. In rheumatoid arthritis, and most other rheumatic diseases, the initiating event or trigger for the disease is not known. NIAMS scientists will continue searching for etiologic factors, such as infectious agents, in joint tissues and fluids of patients with rheumatoid arthritis.

Polymyositis. Polymyositis is an uncommon serious inflammatory muscle disease. NIAMS scientists have been able to categorize patients into subgroups according to the characteristic abnormal antibodies they produce. These groups of patients differ with respect to rapidity of onset of disease, season of onset, clinical manifestations, and, most important, response to therapy. Future studies will focus on understanding further the role that abnormal antibodies play and how they contribute to these differences.

NIAMS scientists are seeking direct evidence for a viral cause of human polymyositis by examining tissues from patients with myositis for evidence of viral inflammation. A better understanding of the transition from acute viral infection to chronic, self-sustaining muscle inflammation in a mouse model will shed light on how a virus could initiate polymyositis.

Bone Metabolism and Fracture Healing. NIAMS researchers have found that several growth factors are synthesized during bone healing. These growth factors are being studied during both normal and impaired fracture repair, including osteoporosis. The estrogen receptor on bone cells is thought to be important in osteoporosis. NIAMS scientists are now using a new technique, polymerase chain reaction, to measure changes in the estrogen receptor. Knowledge gained through these studies will contribute to a better understanding of both bone metabolism and fracture repair, and lead to improved methods of preventing and treating bone disorders, such as osteoporosis.

Clinical Immunology. Having fully characterized the rat receptor for an antibody known as IgE, researchers are turning their attention to duplicating the work in humans. Discovery of the receptor structure should facilitate a systematic search for drugs that can block the initiating event in the allergic reaction, binding of IgE to the receptor, thereby eliminating the symptoms of an allergy attack--sneezing, itching, wheezing and anaphylactic shock. Intramural scientists are beginning the testing of anti-allergy drugs.

Laboratory of Physical Biology. The recent installation of a high-resolution cryo-electron microscope in the Laboratory of Physical Biology makes highly innovative studies possible and facilitates analysis of extremely small structures. In addition to investigating the structure of viral components and their assembly, researchers are examining intracellular protein filaments in the skin. This research will provide insights into skin disorders such as the ichthyoses, in which skin cells are reproduced more rapidly than they are shed, leading to an abnormal accumulation with the appearance of fish scales.

Laboratory of Skin Biology. In January 1990, the NIAMS inaugurated a cellular and molecular biology program for intramural skin research. The primary mission of the new Laboratory of Skin Biology will be to conduct basic research on skin. Investigations will focus initially on the structure and expression of the principal proteins of the epidermis. Physical, electron microscopic, cellular and molecular biological approaches will be utilized. Attempts to create mouse models will be made. The aim of these studies is to understand more fully the various disorders of structural proteins in human skin.

Rationale for the Budget Request

The Intramural Research Program will be funded at $12,922,000 or $845,000 over the 1990 to support increases, including a modest increase in full-time equivalent (FTEs) positions.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Research Management and Support

Authorization: Indefinite.

Budget Authority:

1990 Appropriation		1991 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA
59	$6,724,000	61	$7,643.000	+2	+$919,000

Purpose and Method of Operation

Research Management and Support provides the staff and resources for the scientific direction and overall management of the NIAMS. It encompasses the Office of the Director as well as the Extramural Program activities and involves a wide range of functions, including administrative, scientific, and managerial. Collectively, these provide the leadership and guidance required to evaluate research needs and identify promising research areas for new or expanded investigation.

The Office of the Director provides the guidance and professional leadership for all the Institute's programs. It includes three main staff offices: the Office of Prevention, Epidemiology, and Clinical Applications; the Office of Administrative Management; and the Office of Program Planning and Evaluation. The Office of Prevention, Epidemiology, and Clinical Applications develops and coordinates Institute policies and programs of disease prevention and health promotion, epidemiology and biometry, clinical studies and trials, and technology assessment and transfer. This office is also the focal point of the NIAMS for international cooperative research activities of the Institute. These activities provides an opportunity for U.S. scientists to collaborate with colleagues throughout the world in areas of high priority and mutual interest and benefit such as Lyme disease and osteoporosis.

The Extramural Program includes professional and support personnel who are responsible for administration of the Institute's grant activities. Scientific staff assist in planning and development of programs to pursue research needs in the most efficient and effective manner for areas of Institute responsibility. They also review, award, and administer grants and contracts, providing guidance on scientific programs and ensuring dissemination of research results to the scientific community and the public.

Rationale for the Budget Request

Research Management and Support will be funded at $7,643,000 or $919,000 over the 1990. This year the Office of the Director will initiate a multiyear program for the development of a National Plan for arthritis and musculoskeletal and skin diseases and has committed additional resources for this purpose. An increase in FTE ceiling will allow filling professional and support vacancies in support of the extramural grant programs and for the further development of the prevention, epidemiology and clinical applications programs.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Detail of Permanent Positions

	1989 Actual	1990 Appropriation	1991 Estimate
ES-5	1	2	2
ES-4	2	2	2
GS/GM-15	9	9	9
GS/GM-14	10	10	10
GS/GM-13	4	4	6
GS-12	10	13	14
GS-11	7	7	7
GS-09	2	3	4
GS-08	5	5	5
GS-07	14	15	17
GS-06	8	8	8
GS-05	3	3	3
GS-04	1	1	1
Subtotal	76	82	88
Grades established by act of July 1, 1944 (42 U.S.C. 207):			
Surgeon General Grade	0	0	0
Asst. Surgeon General Grade	0	0	0
Director Grade	5	5	5
Senior Grade	2	2	2
Full Grade	0	0	0
Senior Assistant Grade	0	0	0
Subtotal	7	7	7
Ungraded	1	1	1
Total permanent	84	90	96

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

New Positions Requested

	Grade	1991 Number	1991 Annual Salary
Intramural Research			
Biochemist	GS-13	1	$46,861
Microbiologist	GS-14	1	53,698
Biologist	GS-09	1	25,529
Chemist	GS-09	1	25,529
			151,617
Research Management and Support			
Grants Management Specialist	GS-12	1	37,019
Epidemiologist	GS-12	1	46,861
			83,880

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Advisory and Assistance Services

Consultant services continue to be of critical importance in carrying out the mandates under which we operate. The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) use of consultant services is for the National Advisory Council, the National Advisory Board, and the Board of Scientific Counselors. The appointed members of the congressionally mandated groups provide scientific, medical, and technical expertise to the Institute and perform services that are essential to the review process; by statute, their concurrence is required before most grant awards can be made (section 475 of the Public Health Service Act, 42 USC 289 1-4).

The cost of consultant services increased from $29,000 in fiscal year 1989 to $53,000 in fiscal year 1990, which reflects the expenses of the Board of Scientific Counselors that reviewed the Laboratory of Physical Biology and Orthopaedic Research Unit of the Intramural Research Program. For fiscal year 1991, a minimal increase is expected due to continuation of these responsibilities.

Policy guidelines for internal controls exist in the form of OMB Circular A-120 and DHHS General Administration Manual 8-15. Each year a consultant services plan is prepared identifying planned Advisory and Assistance Services procurement. The NIH accounting system contains Common Account Numbers (CANS) that have been designated for use in identifying and aggregating costs for Advisory and Assistance Services.

MONDAY, MARCH 19, 1990.

NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS

WITNESSES

DR. JAMES B. SNOW, JR., DIRECTOR, NIDCD
DR. WILLIAM F. RAUB, ACTING DIRECTOR, NIH
DR. JAY MOSKOWITZ, FORMER ACTING DIRECTOR, NIDCD
GEOFFREY E. GRANT, ACTING EXECUTIVE OFFICER, NIDCD
PATIENCE T. SPARKS, BUDGET OFFICER, NIDCD
DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DHHS

Mr. NATCHER. At this time we take up the budget request for fiscal year 1991 for the National Institute on Deafness and Other Communication Disorders.

We have before the committee Dr. Snow. Dr. Snow, before you give us your statement, tell us who you have with you there at the table.

Dr. SNOW. Thank you very much, Mr. Natcher.

INTRODUCTION OF ASSOCIATES

To your far right is Mrs. Patience T. Sparks, Budget Officer of the Institute, Mr. Geoffrey E. Grant, Acting Executive Officer. On your left is Dr. Jay Moskowitz, Former Acting Director of the Institute, Dr. Raub, and Mr. Williams.

Mr. NATCHER. Good. Thank you, Dr. Snow. We will be pleased to hear from you.

Dr. SNOW. I would like to present highlights of a longer statement to be published in the record.

Mr. NATCHER. Fine.

OPENING REMARKS

Dr. SNOW. It is a privilege to appear before this committee. In the year and a half since the National Institute on Deafness and Other Communication Disorders was created by the Congress, great strides have been made. We are particularly indebted to Dr. Jay Moskowitz for the able stewardship he provided to the new Institute. Under his superb leadership, a fully functioning administrative staff was assembled and all of the legislative mandates for NIDCD have been initiated or planned. Excellent intramural and extramural scientific programs were transferred to the new Institute and we intend to build on this strong foundation.

Our goal is to maximize the gains that can be realized from research on human communication. We are supporting research across the entire biomedical spectrum from basic research to clinical studies to technology transfer and to prevention and rehabilita-

tion. The basic research is building a foundation for the next generation, while many of the clinical and rehabilitative programs are aimed at helping those with disabilities today, improving their lives. I am very pleased to be able to share with you selections of exciting scientific advances from our areas of science as well as highlights of research plans of the Institute.

The NIDCD is pleased to join with several other institutes at NIH in celebrating the Decade of the Brain. Neurobiology is an important component of our research portfolio both extramurally and intramurally. An example of the focus of NIDCD on neurobiology is neural regeneration. Regeneration of neural tissue after injury or illness occurs in very few places in the human body. Interestingly, olfactory neuroepithelium tissue does have the ability to regenerate. Research in this area has profound implications for repair and regeneration of the nervous system.

Anatomical and physiological damage to the olfactory system appears early in the development of Alzheimer's disease and other serious neurological disorders. The etiology of deficits in olfaction and their predictive value as early warning signs of these diseases are being studied by NIDCD supported investigators.

Scientists supported by NIDCD have utilized the tools of molecular biology and genetics in ascertaining how human communications systems work at a fundamental level. I intend to encourage these areas for development and expansion. Our scientists are committed to identifying the genes and their products responsible for hereditary deafness. This research holds the promise of genetic replacement and interrupting the aberrant process to prevent deafness.

NOISE CONFERENCE

Noise exposure is the most common cause of preventable hearing loss. NIDCD sponsored a Consensus Development Conference on noise and hearing loss at NIH from January 22 to 24th of this year. The statement drafted by the conference panel provided recommendations and avenues for future research related to noise and hearing loss. The NIDCD is planning a major public health educational program on the prevention of noise-induced hearing loss.

Half of our children have ear infections before they reach their first birthday and nine out of 10 children have ear infections by the time they are six years old. Otitis media is the leading cause of acquired hearing loss before age 10. NIDCD is collaborating with NIAID and NICHD in issuing a solicitation for research on a vaccine against otitis media.

RESEARCH ON BALANCE

Millions of Americans, age 17 and older have experienced a dizziness or balance problem. A majority of people over 70 years of age report problems of dizziness and imbalance. Balance-related falls account for more than one-half of the accidental deaths in the elderly. NIDCD is encouraging research aimed at improving our understanding of the causes, treatment and prevention of these disorders that present safety and quality of life issues for elderly Americans.

A new area of balance research has been generated by the space program. A number of research needs must be addressed in this area including space motion sickness among astronauts during the early stages of the mission.

VOICE DISORDER TREATMENT

Institute-supported scientists have made great advances in therapeutic approaches to voice, speech and language disorders. This year investigators in the NIDCD intramural program were the first to demonstrate a successful treatment for voice tremor which affects women primarily and makes speech difficult to understand. Scientists in the speech and voice unit injected botulinum toxin into muscles of the voice box of patients with this disorder and successfully eliminated the tremor. These injections have proved effective also in treating spasmodic dysphonia.

TASTE AND SMELL DISORDERS

An estimated 10 million Americans have taste and smell disorders. There is a natural decline in smelling ability that typically occurs after age 60. Some people are born with chemosensory disorders but most develop them after an injury or illness. Loss of the senses of smell and taste can also be caused by exposure to certain chemicals and medicines. A person with these problems is deprived of an early warning system most of us take for granted. Smell and taste alert us to fires, poisonous fumes, leaking gas and spoiled food.

The NIDCD intramural research program is a strong one and is widely recognized for its ground breaking research through basic and clinical studies. I hope to develop this program further to include units of excellence in each of our areas of science. I intend for our intramural program to provide a model to the scientific community in molecular biology and molecular genetics, to conduct clinical trials of promising new therapies, and to serve as a national training resource.

NATIONAL STRATEGIC RESEARCH PLAN

Last year we reported to you on the research plan for the Institute, the National Strategic Research Plan. This year we are analyzing our research grant portfolio relative to the plan, looking for areas that need particular Institute emphasis. In addition this year we have a second plan, one for training. There remains a shortage of trained investigators in our disciplines. In July of 1989, NIDCD convened a panel of expert consultants to identify critical research training activities. The report from this panel included a number of valuable and specific recommendations. We are implementing a number of these recommendations including the establishment of the Physician Scientist Award. Special emphasis will be placed on research training of underrepresented minorities and communicatively-impaired individuals. We are developing a third plan for acquiring sound epidemiologic data in each of the areas within the NIDCD mission.

The NIDCD will initiate a new centers program through two mechanisms. We plan to award National Multipurpose Research

and Training Centers to support basic and clinical research, research training, continuing professional education, and dissemination of information to the public. The NIDCD will use an innovative mechanism to widen the opportunity for more institutions to participate in the centers program. This mechanism is the Exploratory Grants Program which encourages institutions with limited experience in multi-disciplinary research to develop and test such a program.

INFORMATION CLEARINGHOUSE

The Institute has undertaken a number of activities toward the development of an information clearinghouse including a major successful meeting in October 1989 that identified gaps in information as well as existing sources of information. The goal of this clearinghouse is to be an Institute resource where the results of the latest studies funded by NIDCD are made available to the public, researchers, professionals and organizations.

In closing, I would like to note that we live in the information age. Never before has the ability to communicate effectively had such a major effect on the individual's economic and social well-being. NIDCD is committed to excellence in research, maximizing the benefits of research advances and making available the latest technology to Americans who would benefit most, the communicatively handicapped. The scientific community is responding to this new Institute in the typical American "can-do" attitude. The Institute will make every effort to make sure the latest information from research is known to the afflicted, the public, the medical profession, and other scientists.

Mr. Chairman, the fiscal 1991 budget request is $122,847,000. I will be pleased to try to answer any questions you might have.

Mr. NATCHER. Thank you, Dr. Snow.

[The information follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Institute on Deafness and Other Communication Disorders

I am honored to appear before this Committee as the first permanent Director of the National Institute on Deafness and Other Communication Disorders (NIDCD). In the year and a half since the Institute was created by the Congress great strides have been made. We are particularly indebted to Dr. Jay Moskowitz for the very able stewardship he provided for the new Institute. Under his superb leadership, a fully functioning administrative staff was assembled and all of the legislative mandates for the NIDCD have been initiated or planned. Excellent extramural and intramural scientific programs were transferred to the new Institute and we intend to build on that strong foundation. Our goal is to maximize the gains that can be realized from research on human communication. We are supporting research across the entire biomedical spectrum, from basic research to clinical studies to technology transfer and to prevention and rehabilitation. The basic research is building a foundation for the next generation, while many of the clinical and rehabilitation programs are aimed at helping those with disabilities today, improving their lives. I am very pleased to be able to share with you selections from exciting scientific advances from our areas of science as well as highlights of research plans of the Institute.

The NIDCD is pleased to join with several other Institutes at the NIH in celebrating the Decade of the Brain. Neurobiology is an important component of our research portfolio, both extramurally and intramurally. The NIDCD observed its first anniversary this October and elected to celebrate with a scientific lecture on the cutting edge of neurobiology and auditory research. An example of the focus of NIDCD on neurobiology is in neural regeneration. Regeneration of neural tissue after injury and illness occurs in very few places in the human body. Interestingly, nasal neuroepithelium is one tissue that does have the ability to regenerate. As scientists supported by the NIDCD seek to unlock the clues to why olfactory tissue has this ability, the information they learn can be applied to other nonregenerative tissues. Other NIDCD-supported researchers have determined that olfactory neuroepithelium is a source of renewal of olfactory receptor neurons, which have a powerful nourishing effect on the brain, and can be a direct source of additional cells for the brain. Scientists are now identifying the characteristics of these cells. These findings have profound implications for the repair and regeneration of the nervous system.

Anatomical and physiological damage to the olfactory system appears to occur early in the development of Alzheimer's and other serious neurological diseases. The etiology of deficits in olfaction and their predictive value as early warning signs of these diseases is being studied by NIDCD-supported investigators.

Scientists supported by the NIDCD have utilized the tools of molecular biology to uncover important information on how human communication systems work at a fundamental level. This is an area

I intend to encourage for development and expansion. NIDCD scientists have uncovered important information on the molecular biology of cochlear outer hair cell motility which plays an important role in hearing by modulating the micromechanical properties of the hearing organ. These scientists have recently defined one of the mechanisms that regulates the movements of the outer hair cell. I believe the time is ripe to exploit also the particular opportunities that exist in molecular genetics. Scientists are moving closer to identifying the genes and their products responsible for hereditary deafness. This research holds the promise of genetic replacement and interrupting the aberrant process to prevent deafness.

Noise exposure represents the most common preventable cause of hearing loss today. The NIDCD sponsored a Consensus Development Conference on Noise and Hearing Loss at the NIH on January 22-24, 1990. The statement drafted by the conference panel provided recommendations and avenues for future research related to noise and hearing loss. Among the topics the Panel recommended for future research are investigations into the mechanisms underlying noise-induced hearing loss and the evaluation of the efficacy of hearing conservation programs. The NIDCD is planning a major public health educational program on the cause and prevention of noise induced hearing loss.

Half of our children have ear infections before they reach their first birthday, and nine out of 10 children have ear infections by the time they are 6 years old. Otitis media is the leading cause of acquired hearing loss before age 10. The NIDCD is collaborating with the NIAID and the NICHD in issuing a solicitation for research on a vaccine against otitis media.

Perilymphatic fistulas are fluid leaks through defects in one or both of the small windows between the middle and inner ears. The symptoms include dizziness, ringing in the ears, and hearing loss. Considerable controversy surrounds the diagnosis of perilymphatic fistula. The NIDCD will issue a Request for Applications (RFA) to study the differential diagnosis of perilymphatic fistula, seeking a diagnostic marker for perilymph fluid that would confirm the presence of a leak, as well as other clinical aspects of perilymphatic fistulas.

Congenital cytomegalovirus (CMV) is a well-established cause of disorders of the auditory, visual, and central nervous systems. New evidence suggests that "quiescent" CMV may play a role in the development of perilymphatic fistulas and Meniere's disease (a disorder that affects the inner ear and causes episodes of vertigo, fluctuating hearing loss, and a roaring sound in the ears). Other studies will focus on CMV in AIDS patients to determine whether the deafness and communication disorders often reported among those patients are due to the CMV or to the AIDS virus. The population that is particularly in need of study are the pediatric AIDS patients. The NIDCD will begin its support of research on the effect of AIDS in communication systems in FY 1991.

Millions of Americans age 17 and older have experienced a dizziness or balance problem. Several groups of people are particularly at risk for different reasons. A majority of people

over 70 years of age report problems of dizziness and imbalance, and balance-related falls account for more than one-half of the accidental deaths in the elderly. The NIDCD is encouraging research aimed at improving our understanding of the causes, treatment, and prevention of these disorders that present safety and quality of life issues for elderly Americans. A new area of balance research has been generated by the space program. A number of research needs must be addressed in this area, including space motion sickness among astronauts during the early stages of the mission.

Institute-supported scientists have made great advances in therapeutic approaches to speech, voice, and language disorders. This year, investigators in the NIDCD intramural program were the first to demonstrate a successful treatment for voice tremor, which affects women primarily and makes speech difficult to understand. Scientists in the Speech and Voice Unit injected botulinum toxin into muscles of the voice box of patients with this disorder and successfully eliminated the tremor. Botulinum toxin injections have also proven to be effective in treating another voice disorder, spasmodic dysphonia, which has been treated by cutting one of the nerves to the larynx. In another exciting advance this year in our extramural program, a new treatment, photodynamic therapy, has been found to be effective for recurrent laryngeal papillomavirus infections. Other conventional and experimental therapies including vaccines and interferon failed to cure this disease. This represents a promising new therapy for a difficult to control and life-threatening disease.

An estimated 10 million Americans have taste and smell disorders. A predominant problem is the natural decline in smelling ability that typically occurs after age 60. Some people are born with chemosensory disorders, but most patients develop them after an injury or illness. Loss of the senses of smell and taste can also be caused by exposure to certain chemicals and by some medicines. A person with faulty senses of taste and smell is deprived of an early warning system that most of us take for granted. Smell and taste alert us to fires, poisonous fumes, leaking gas, and spoiled foods. In addition to a reduction in quality of life for those unable to smell or taste, the loss of these senses can be associated with nutritional deficiencies in the elderly. Interest in and enthusiasm for eating are much reduced in those who cannot smell or taste their food.

The NIDCD Intramural Research Program is a strong program that is widely recognized for its ground breaking research through basic and clinical studies. I hope to develop this program further to include units of excellence in each of our areas of science. I intend for our intramural program to provide a model to the scientific community in molecular biology and molecular genetics, to conduct clinical trials of promising new therapies and to serve as a national training resource.

Last year we reported to you on the Research Plan for the Institute -- the National Strategic Research Plan. This year we are analyzing our research grant portfolio relative to the Plan, looking for areas that need particular Institute emphasis. In addition, this year, we have a second Plan, one for training.

There remains a shortage of trained investigators in our fields. In July 1989 the NIDCD convened a panel of expert consultants to identify critical research training activities that could be implemented by the NIDCD in three time periods: the next one to two years, five years from now, and 10 years from now. The report from this panel included a number of valuable and specific recommendations. We are implementing a number of these recommendations including establishment of a Physician Scientist Award. Special emphasis will be placed on research training of underrepresented minorities and communicatively-impaired individuals. We are developing a third plan for acquiring sound epidemiologic data in each of the areas within the NIDCD mission.

The NIDCD will initiate a new Centers program through two mechanisms. We plan to award National Multipurpose Research and Training Centers to support basic and clinical research, research training, continuing education for health professionals, and dissemination of information to the public. The NIDCD will use an innovative mechanism to widen the opportunity for more institutions to participate in the Centers program. This mechanism is the Exploratory Grants program, which encourages institutions with limited experience in multidisciplinary research to develop and test such a program.

The Institute has undertaken a number of activities toward the development of an information Clearinghouse, including a major, successful meeting in October 1989 that identified gaps in information as well as existing sources of information. The goal of this Clearinghouse is to be an Institute resource where the results of the latest studies funded by the NIDCD are made available to the lay public, researchers, professionals, and organizations.

In closing , I would note that we live in the information age. Never before has the ability to communicate effectively had such a major effect on the individual's economic and social well-being. The NIDCD is committed to excellence in research and to maximizing the benefits of research advances and making available the latest technology to Americans who would benefit most, the communicatively handicapped. The Institute will make every effort to ensure that the latest information from research is known to the afflicted, the public, medical professionals, and other scientists.

Mr. Chairman, the FY 1991 budget request is $122,847,000. I will be pleased to answer any questions you might have.

RESEARCH PRIORITIES

Mr. NATCHER. Now, doctor, as the institute's first permanent director what will be your personal priorities in the next several years?

Dr. SNOW. My personal priorities are research project grants, training, and the national Multi-purpose Research and Training Centers. They are my highest priority. We want to exploit the state of the art in molecular genetics in disorders of human communication that are clearly hereditary. We want to prevent hearing loss from known causes such as loud noise and ototoxic drugs. We want to rehabilitate the hard of hearing with better hearing aids. We want to improve diagnosis of vestibular problems. We want to develop treatment strategies for losses of the senses of smell and taste and we want to develop new drug therapy for aphasia.

HEREDITARY DEAFNESS

Mr. NATCHER. The Institute's long range research plan identifies a broad mandate. How can you be sure that your dollars are not spread too thinly pursuing too many research areas?

Dr. SNOW. I think we have to concentrate on the most important problems. From my point of view, those include the prevention of hereditary deafness, the application of neural regeneration found in the olfactory neuroepithelium to the maturation and repair of the nervous system and reduction of the average age at which the diagnosis of congenital deafness is made from two and a half years to nine months.

Mr. Chairman, when I graduated from medical school 34 years ago the average age at which a deaf child was diagnosed was three years. Currently it is two and a half years. In that 34 years we have only made progress of six months. Yet, it is important that the diagnosis be made well before two years of age because at that age the learning curve for language begins to fall off. Yet we have the technology available to make the diagnosis of a profound loss of hearing within the first week of life.

Let me show you what we want to do. We want to reduce the average age at which the diagnosis is made. Here is a youngster, an infant less than six months of age, already fitted with a hearing aid as he should be so that he can begin to learn language by using his residual hearing. (Figure 1)

AN INTENSE DESIRE TO LEARN LANGUAGE

Figure 1

Dr. SNOW. We either have to begin amplification and special education early or, if there is no residual hearing, to begin special education early so that these youngsters will learn language in a timely fashion.

Mr. NATCHER. Dr. Snow, does the plan identify the cost of its recommendations?

Dr. SNOW. No. We do not have a specific cost for each of these areas. They depend largely upon scientist-initiated proposals, so that is difficult to do.

Mr. NATCHER. Has the institute developed a plan which will eventually allocate a certain portion of its budget to each program area and to each research mechanism such as centers, grants, in-house research?

Dr. SNOW. We do have that kind of a proposal. We have not broken it down into the seven areas that the institute serves: hearing, balance, smell, taste, voice, speech and language.

I can tell you that approximately 57 percent of our resources go to the areas of hearing and vestibular function, 27 percent go to voice speech and language and 16 percent go to the chemical senses.

RECRUITMENT PROBLEMS

Mr. NATCHER. Dr. Snow, as the first person recruited from outside NIH to be an Institute director for some time, I wonder if you could share your thoughts with the committee about the NIH recruitment problem and what caused you to take the job?

Dr. SNOW. This new institute is the most attractive enterprise that I have seen in my career. It was my desire to participate in this exciting work that made my decision easy. However, it will be difficult to recruit senior scientists at the associate professor or higher level because of low salaries and limited portability of benefits. Fortunately, with this most attractive enterprise, we will be able to recruit the best to this important work.

FY 1990 APPROPRIATION

Mr. NATCHER. In 1990 the Institute received almost $18,000,000 above the President's request. In what areas did you concentrate the additional funds, Doctor?

Dr. SNOW. We concentrated those in the three major priorities of this committee. We specifically placed $6,000,000 in competing grants, $5,500,000 in the new National Multipurpose Research and Training Centers and $800,000 in minority programs.

We also placed $500,000 in training, $700,000 in career development, $1,000,000 in contracts, and the balance we used for staffing the Institute and for developing the intramural research program.

RESEARCH TRAINING

Mr. NATCHER. If an adequate number of researchers is important for the deafness field, why does the Institute budget straight line funding for research training?

Dr. SNOW. Certainly research training is of the highest priority with us. It is important that we, particularly in this new Institute, devote our attention to research training. The budgetary reality

that you mentioned has to do with the competing needs and requirements for these resources.

Mr. NATCHER. The Institute convened an expert panel on research training last year. What recommendations did the panel make for the next five years, Dr. Snow?

Dr. SNOW. They recommended that we increase the knowledge of undergraduates in research careers in the fields of the communication sciences. They recommended that the period of training for new investigators at the post-doctoral level be two years or more. They recommended that we implement the Physician Scientist Award, and they recommended the Mentor Award, an innovative approach to training in which a supplement could be given to a well-established, outstanding investigator who had a research project grant supported by the Institute and that training could be done in conjunction with that project.

Mr. NATCHER. I yield to Mr. Conte.

Mr. CONTE. Thank you, Mr. Chairman.

Dr. Snow, you are at the helm of the newest ship of the NIH fleet. There is a lot of promise for deafness research at your institute.

First of all, I want to take this opportunity to welcome you to your new responsibilities as the director of NIDCD.

Dr. SNOW. Thank you, sir.

Mr. CONTE. You have an outstanding clinical and research background and you are respected in the medical community for all your work at the University of Pennsylvania. You will, no doubt, learn the ropes quickly here in Washington and forge ahead with I think very exciting new programs in the future.

Dr. SNOW. Thank you.

WAARDENBURG SYNDROME

Mr. CONTE. Can you share with us your views on where the greatest opportunities in research lie in the year ahead and what will you be doing to take advantage of those opportunities?

Dr. SNOW. I think in all these areas we have a great opportunity in molecular biology and molecular genetics. Much of the knowledge that has come about in these seven areas has come through anatomy, physiology, electrophysiology, and psychophysics. The field has now developed in molecular biology and particularly in molecular genetics to where a great deal of new information can come forth very readily. We are going to be taking advantage of this opportunity.

Let me show you what sort of things that we are working on at the present time. Here is a picture of a mother and her baby. (Figure 2)

WAARDENBURG SYNDROME

Waardenburg Syndrome is one of the most common syndromic causes of hereditary deafness. We will soon have the cell lines from a child with Waardenburg Syndrome to search for the gene.

Patients illustrated are part of a genetic and molecular study of Waardenburg Syndrome being conducted by Dr. James H. Asher, Jr. and Dr. Thomas B. Friedman of the Department of Zoology and Genetics at Michigan State.

FIGURE 2

Dr. SNOW. The mother has a loss of hearing in both ears, profound in one ear and fairly severe in the other. These are her two children. As you will notice each member of the family has a white forelock. The baby has a profound loss of hearing in both ears. The older child also with a white forelock has a profound loss of hearing in both ears. Note that this youngster has one blue eye and one brown eye. This is the condition in Waardenburg Syndrome. This is one of the hereditary causes of deafness that we think will yield to molecular genetic approaches. This baby is fortunate. There is a clear sign with the white forelock that he might have a loss of hearing. So the diagnosis can be established very early.

What we are doing in this is searching for the gene responsible for Waardenburg Syndrome. We are spurred on by the fact that in retinitis pigmentosa, which causes blindness and deafness, the gene has been found by one of the investigators supported by NIDCD. We have a team now working in the intramural program. We have received a cell line from Japan of a child with Waardenburg Syndrome and we are very hopeful the gene for Waardenburg Syndrome can be found too.

Once we know what the genes are, we can find out what their products are and develop strategies for intervening and preventing the development of deafness.

Mr. CONTE. You mentioned a couple of times about the white forelock as if that really was significant. What does that mean?

Dr. SNOW. Well, it is one of the characteristics of Waardenburg Syndrome. There are individuals with a white forelock who have a loss of hearing and some who do not. Some individuals with a white forelock develop premature graying. These pigmentary characteristics, one blue and one brown eye and the white forelock, tip us off. It is the easiest one of the congenital hereditary hearing losses to diagnose because it shows on the outside. Virtually all of the other forms of hereditary deafness do not show on the outside. Unfortunately, the diagnosis of hearing loss is often not made until two and a half years of age when the child is not developing speech as he or she should have well before that age.

BUDGET REQUEST

Mr. CONTE. What was your initial fiscal year 1991 request?

Dr. SNOW. Our original request was $142,641,000 without AIDS.

Mr. CONTE. In your professional judgment, is the 1991 budget put forward today adequate to carry out your long range objectives and if additional funds were provided, tell us where you would put the money.

Dr. SNOW. Well, in my professional judgment the budget of $122,874,000 is not adequate to take care of all of the opportunities that are present to us in making progress in this area.

If I were to have the opportunity to add additional funds to this budget, I would make as my first priority adding to the research centers. We are currently budgeted to fund three to five of these Multipurpose Research Centers during fiscal 1990. Unless that budget is increased, we would not be able to fund any additional centers during fiscal 1991. So that would represent my first priority.

I would recommend an increase in the research project grant category. We are going to be able to fund only 102 competing research project grants during fiscal 1991 but in my professional judgment 153 high-quality and worthy research project grants should be funded.

I think it is important also that we increase research training. We recognize a need for additional scientists and we would add in that area. I would also favor adding in the contract area because we are not going to be able to start any new clinical trials in fiscal 1991 with the budget that I have presented.

STAFFING NEEDS

Mr. CONTE. As the newest Institute you might encounter unique start up problems in budget and organization. What problems have you encountered in building the new Institute and what in your professional judgment are your long-term staffing needs over the next five years. If you don't have that, you can put that in the record.

Dr. SNOW. I would just like to say that we have made excellent progress in accomplishing what we have set out to do. We have a fully functioning Institute at the present time. We are gradually becoming independent of the operation of the Neurology Institute except we still depend on the Neurology Institute for their contract office work.

That is likely to be solved in the coming year. We are very pleased to have a Budget Officer, a Chief of Program Planning and Health Reports Branch and the Executive Director of the national advisory board.

We are recruiting for a number of senior level positions including the scientific director, the clinical director, the director of the division of the extramural activities and the executive officer.

Mr. CONTE. Could you provide for the record what the impact of last year's sequester on your Institute was and what projects cannot get funded as a result of the sequester?

Dr. SNOW. Yes, we will put that in the record.

Mr. CONTE. Thank you, Mr. Chairman.

[The information follows:]

EFFECT OF SEQUESTRATION

The amount of sequestration under P.L. 101-239 for the National Institute on Deafness and Other Communication Disorders was $1,256,000. An estimated $1,136,000 was sequestered from research project grants. Noncompeting research project grants will be negotiated 9.3 percent and competing grants will be negotiated 10.6 percent.

Approximately $30,000 was sequestered from the Research Career program, and $33,000 was withheld from the National Research Service Award training programs. This will result in the reduction of one full time training position. From Research and Development Contracts, $21,000 was sequestered; from the Intramural Research Program, $18,000; from Research Management and Support, $2,000; and from the Extramural Construction Program, $16,000.

By carefully reviewing all research project grants administratively and applying downward negotiation rates, we are not planning to reduce the number of grants supported. We believe that as the newest Institute at the NIH, it is important that we provide as much support as possible to our scientific community.

Mr. NATCHER. Mr. Stokes, I yield to you.

Mr. STOKES. Dr. Snow, it is a pleasure to join my colleagues in welcoming you before our subcommittee.

Dr. SNOW. Thank you very much, Mr. Stokes.

NOISE-INDUCED HEARING LOSS

Mr. STOKES. Doctor, are Americans very knowledgeable as to what noises place us most at risk for hearing loss?

Dr. SNOW. I do not think there is good general knowledge about it. Any sound that is 85 decibels or higher has the potential of damaging the hearing. If that exposure is for more than a few hours, there is risk that damage is being done. We need to engage in a major educational campaign, and we need to start that with school children. A lot of the damage that occurs begins, particularly in boys, between 10 and 20 years of age. We need to start before that period.

Mr. STOKES. What noises, for instance, places us most at risk for hearing damage?

Dr. SNOW. Any internal combustion engine makes sufficient noise to cause damage, wood working equipment, chain saws, outboard motors, most industrial mechanized activities involve sufficient noise to be damaging.

Mr. STOKES. Do you have any plans for some type of public education program relating to this?

Dr. SNOW. Yes, sir. We plan to launch a major public health education program on noise-induced hearing loss in the fall of this year.

HEARING LOSS IN MINORITIES

Mr. STOKES. Doctor, are minorities disproportionately affected by hearing and speech disorders?

Dr. SNOW. Yes, they are. In noise-induced hearing loss, because of the nature of the work many minority individuals do tend to be exposed to more noise than the general population.

Likewise in areas of infection such as otitis media, because of the lack of readily available health care, they may suffer relatively more from infections like otitis media than the general population.

Mr. STOKES. Does your institute have any specific plans for addressing this situation?

Dr. SNOW. Yes, indeed. We have several centers that focus on otitis media. We have individual research projects that address these subjects. In our Multi-purpose Research and Training Centers there is a call in the request for proposals for minority studies, that is studies to be conducted within minority groups and also for the recruitment of minorities to the professional staff.

Mr. STOKES. What percentage of your budget is targeted toward minorities, particularly in the area of speech impairments and hearing disorders?

Dr. SNOW. The overall total for the 1991 fiscal year is $1,100,000. A portion of that is in Minority Biomedical Research Support; there is $326,000 in that. We have another $500,000 budgeted for minority supplements to research project grants. We have already awarded five of these and are well on our road to utilizing what has been budgeted for fiscal 1990. I believe that we will accomplish

that by the end of this fiscal year. We are requesting an additional $500,000 for 1991.

Then we have some research project grants that are speech related in minority populations. In the aggregate we are spending $272,000 for those studies.

Mr. STOKES. So overall are you able to give us a percentage in terms of your overall budget?

Dr. SNOW. I would like to provide the exact percentage for you in the record. But I can estimate that it is approximately 1 percent.

Mr. STOKES. For the record would you provide us the exact percentage?

Dr. SNOW. Yes, sir.

[The information follows:]

MINORITY RELATED RESEARCH

The National Institute on Deafness and Other Communication Disorders (NIDCD) will support approximately $1,100,000 in minority related research in FY 1991, which is nine-tenths of one percent. Minority related research supported by the NIDCD includes the Minority Biomedical Research Support program and Minority supplements to research project grants. In addition, the NIDCD has made a concerted effort to include minority populations in its research programs. In several of our clinical trials on otitis media, specific attention has been made to include minority and communicatively-impaired populations.

LANGUAGE IMPAIRED CHILDREN

Mr. STOKES. Doctor, what is meant by the term "language impaired children"? What are the causes of language impairment and what implications does it have for the academic ability of these children?

Dr. SNOW. It has recently been recognized that there is a condition called "specific language impairment." This represents a sizable portion of the school aged children and the pre-school children. We do not know the exact proportion. One of the things that we want to do is an epidemiologic study to find out the answer to that. These children can be identified as early as four years of age. It turns out that they have difficulty with reading and writing when they are eight years old and many are at a severe academic disadvantage.

COMMUNICATION DISORDERS: AIDS PATIENTS

Mr. STOKES. Doctor, to what extent are AIDS patients affected by communications disorders? You noted that the Institute is conducting research in this area, can you tell us about it?

Dr. SNOW. Yes, sir. AIDS has a devastating effect on the ability of the individual to communicate. It results in a loss of hearing. That is particularly true in the pediatric AIDS patient. We are not certain whether this loss of hearing is due to the AIDS virus itself or to the cytomegalovirus which individuals with AIDS acquire as opportunistic infections.

Since it may be the cytomegalovirus that is causing the loss of hearing, we have stimulated and are supporting a group of investigators at the University of California at San Diego who have developed an animal model that allows the passage of the CMV through

the placenta in guinea pigs. We hope to come to an answer to this question through that research.

Another important area of research in communication in children with AIDS is the study of otitis media in AIDS patients in New York that is being conducted by Dr. Robert Ruben.

SENSE OF SMELL

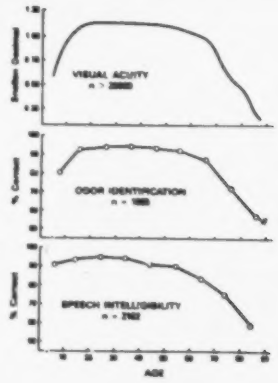
Mr. STOKES. The brochure that you provided us tells us females have a more acute sense of smell than males throughout the age span. Can you tell us about that?

Dr. SNOW. Yes, sir. Through the support of this Institute we have developed a way of measuring the sense of smell in a very satisfactory way. Part of the lack of progress in the sense of smell in the past had been the inability to measure the sense easily as we have been able to do with hearing, for example. (Figure 3)

SENSE OF SMELL

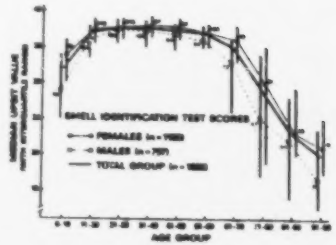
Loss of Smell with Age

The loss of sense of smell with aging parallels the diminution of hearing and vision with age.



Female Superior Sense of Smell

Females have a more acute sense of smell than males throughout the age span.



NIDCD Grantee - Dr. Richard Doty, Department of Otorhinolaryngology and Human Communication and Physiology, School of Medicine, University of Pennsylvania.

FIGURE 3

Dr. SNOW. With this smell identification test, it is possible to test the sense of smell throughout the age span, and at all ages females have a more acute sense of smell than males. Males are represented by the green line here. Females are represented by the blue line. You can see even with young children, girls have a more acute sense of smell than boys.

The striking thing is that at age 65 the sense of smell begins to fall off. The loss of the sense of smell parallels the loss of the sense of vision and also the loss of hearing. Actually, it is a very comparable loss for the three senses.

These data were developed from a large population. When a patient presents with the complaint of a loss of sense of smell, their sense of smell can be measured and compared to what is normal for their age and gender. What would be normal for someone, let's say 70 years of age, is not the same as for someone who is 40 years of age. So it is essential to have this kind of information in order to make progress. These data were developed through the support of our Institute.

Mr. STOKES. Thank you.

APPROVAL RATE

Mr. NATCHER. Dr. Snow, the Institute's grant approval rate in 1989 was 100 percent and is still one of the highest at NIH. Is this appropriate for a developing research field?

Dr. SNOW. The approval rate in our Institute is very high. It ranges from 95 to 97 percent. That is more or less comparable to the other Institutes at NIH. Yes, that is appropriate for our Institute even though it is new.

INTRAMURAL RESEARCH

Mr. NATCHER. How much do you expect your in-house research effort to grow in the next five years?

Dr. SNOW. It should grow in a number of different ways. It is important that we develop units of excellence in each of the scientific disciplines that the Institute serves. Currently, we have a very good program in the hearing area. That needs to be developed and expanded. We also have a very excellent intramural program in voice and speech. We need to develop programs in balance and in smell and taste. These are areas that lend themselves well to molecular biological approaches. These approaches have not been utilized sufficiently throughout the country, and we need to demonstrate to the scientific community where large pay-offs can be made in the coming decade.

Mr. NATCHER. Mr. Conte.

DECADE OF THE BRAIN

Mr. CONTE. Thank you, Mr. Chairman.

Doctor, the Decade of the Brain as you may have heard from your fellow directors, was passed by the Congress, signed into law by the President last year. This is intended to stimulate neurological research at NIH. A number of Institutes are going forth with programs and activities which will improve public recognition of brain related diseases.

Do you have any thoughts on how your Institute might be involved with the Decade of the Brain and do you have any current activities underway with other Institutes related to the decade?

Dr. SNOW. Yes, sir. Neurobiology is a very important part of our work because we deal with the special senses of hearing, balance, smell and taste and all of these are connected to the brain. From the other side of human communication, voice, speech and language, it is also all connected to the brain. So neurobiology amounts to a large part of our work. As a matter of fact, of this current year's budget, $47,000,000 is related in one way or another to neurobiology. The special opportunity that we have to make important contributions to the understanding of the nervous system is in neural regeneration because the olfactory neuroepithelium has this unique ability to be renewed throughout the course of a human's lifetime. We need to learn how this comes about so that it can be applied to the treatment of injuries to the nervous system. What we learn about that may be of importance in disease processes such as stroke and spinal cord injury.

Mr. CONTE. Are you meeting with the other Institutes about this?

Dr. SNOW. Yes, sir, indeed. As a matter of fact, we will be cosponsoring Consensus Development Conferences on acoustic neurinomas with the Neurology Institute and one on botulinum toxin therapy. We are collaborating with the NIAID and the NICHD in the request for proposals for the vaccine for otitis media.

COCHLEAR IMPLANTS

Mr. CONTE. Last year they showed us a cochlear implant device. It fascinated me at that time. Can you tell us what is new in the realm of cochlear implants and are there any remarkable improvements over last year or are we in the same position?

Dr. SNOW. I think the technology in cochlear implants is the same as it was last year. We are supporting contracts with investigators at Melbourne University on developing an improved cochlear implant for the implantation in children, producing a smaller version of what has been used in adults.

Another technologic advance that has occurred is the development of digital hearing aids. We have one of those with us that has been placed in a special container so that one can see the interior of it. I might just pass that up to you.

We are supporting the next stage of advances in cochlear implants in reimplantation that will probably be necessary. Sometimes these implants fail, they stop working and they have to be replaced. The alternatives exist of either implanting the other ear or replacing the one that has been implanted.

Mr. CONTE. Mr. Chairman, I have a lot more questions. I will put them in the record.

Mr. NATCHER. Okay.

Mr. Stokes.

Mr. STOKES. Dr. Snow, at the end of your formal statement you make a very poignant statement, you said, "In closing I would note that we live in the information age, never before has the ability to communicate effectively had such a major effect on the individual's economic and social well-being."

I think that is a very poignant statement about what is occurring today. In 10 years we will move into the next century and at that time one-third of the entrants into the workplace will be minorities.

In the year 2020, 39 percent of the workplace will be minorities. When we consider questions I asked earlier about the disparities between minorities and the majority population and we consider that in your Institute you are devoting 1 percent of your budget to the programs targeted toward eradicating this disparity, it would seem that if we continue at that rate, in 10 years we will not have made very much of an impact on the situation, will we?

Dr. SNOW. No, we will not.

Mr. STOKES. Thank you, Doctor.

Dr. SNOW. Thank you.

Mr. STOKES. Thank you, Mr. Chairman.

Mr. NATCHER. Dr. Snow, we want to thank you and your associates for appearing before our committee at this time in behalf of your budget request for fiscal year 1991. I want to wish you the best of everything, Dr. Snow. It has been a good hearing.

Thank you, very much.

Questions Submitted by the Subcommittee

RESEARCH CENTERS

Mr. Natcher. How many applications has the Institute received for the new comprehensive research centers? How many will be funded in 1990 and at what average cost?

Dr. Snow. The Request for Applications for the new National Multipurpose Research and Training Centers (RTC) was issued in December 1989. By January 1990, 85 inquiries regarding submitting an application had been received. Application receipt date was March 22, 1990, and we have received approximately twenty. We are anticipating funding three to five awards in FY 1990 at an average cost of $1.2 million.

Mr. Natcher. Have you considered changing the research emphasis of the nine ongoing centers you inherited from the Neurology Institute as they come up for re-competition?

Dr. Snow. It is our expectation that at least some of the ongoing centers may apply for the new Multipurpose Research and Training Centers (RTC) as their current grant period ends. They will be considered by the peer review process along with all the other RTC applications received. However, it will be important to maintain the research in the current portfolio of centers.

Mr. Natcher. How many centers will be re-competed in 1991?

Dr. Snow. Two comprehensive centers will recompete in FY 1991.

INSTITUTE STAFF

Mr. Natcher. What will be your end-of-year onboard staff strength in 1990 and 1991?

Dr. Snow. Our FY 1990 end-of-year onboard staff is expected to be 65; for FY 1991, it is estimated to be 69.

Mr. Natcher. Will you reach a full staffing level by the end of 1991?

Dr. Snow. During FY 1991, we are planning to hire a senior scientist, a molecular biologist and two technicians in our Laboratory of Molecular Genetics. The primary function of this laboratory will be to study the genetic factors related to deafness, hearing impairment, and speech, voice, olfactory and vestibular disorders.

INFORMATION CLEARINGHOUSE

Mr. Natcher. What does your 1991 budget include for the information clearinghouse?

Dr. Snow. We anticipate spending $500,000 in the startup phase of the NIDCD Clearinghouse in FY 1990, with an additional $500,000 in FY 1991.

Mr. Natcher. Will the research findings distributed through the clearinghouse also be available through the National Library of Medicine?

Dr. Snow. The Institute staff is coordinating with the National Library of Medicine staff to establish the appropriate cooperative information exchange to ensure the best possible access to information from the Library and the Clearinghouse in the fields of communication disorders.

EDUCATION ON HEARING AND SPEECH DISORDERS

Mr. Conte. Along with biomedical research, outreach and education are important elements of improving hearing and speech health. What efforts are being made to educate both health professionals and the general public on hearing and speech disorders?

Dr. Snow. In both our National Multipurpose Research and Training Centers and our Information Clearinghouse, we are emphasizing the education of health professionals and the general public on the topics of hearing, balance, speech, voice, language, taste, and smell. Both mechanisms will provide major public outreach programs of information and referrals for the public. The Research and Training Centers will also provide the most current continuing education for health professionals in the fields of communication sciences.

RESEARCH TRAINING

Mr. Conte. I am concerned that only 50 E.N.T. doctors are currently engaged in research in this field. I wonder how this field will grow if so few M.D.s are involved. We need to make progress in both the clinical and scientific aspects of deafness research. How can we improve the supply of research oriented E.N.T. physicians?

Dr. Snow. The NIDCD agrees that the number of otolaryngologists actively engaged in basic and clinical research needs to be increased. To address this problem and others related to training, a group of advisors met in July 1989 and recommended that the Institute encourage the use of a three-month training mechanism already in place at NIH. It would be used in conjunction with the Institutional National Research Service Awards (NRSA) to allow physicians to be assigned to three months or more of research exposure in the laboratory of a basic scientist or as an assignee to a clinical investigator. Currently supported NRSA Training Directors will need to apply for these short-term training appointments as supplements to their existing awards and potential applicants will be notified that such appointments will be available.

Another recommendation of the 1989 training meeting was inclusion of the Physician Scientist Award among NIDCD's career development awards. In brief, it is designed to support newly trained clinicians appointed by an institution for development of independent research skills and experience in a fundamental science within the framework of an interdisciplinary research and development program. The award is intended to provide up to five years support of consecutive full-time 12-month appointments, starting with two years of a basic science learning experience and finishing with three years of intensive research under the guidance of a qualified sponsor.

The results of initiating these opportunities for research training of physicians will probably not be realized for 7 to 10 years. Nevertheless, they need to be started as soon as possible.

Mr. Conte. Your budget documents say that your institute gathered a panel of experts to look at this problem. Can you tell us what were the key recommendations?

Dr. Snow. The panel of experts recommended that physicians receive appointments of no less than two years and preferably three years, when they are selected for training on an Institutional National Research Service Award. Trans-NIH data show that success as an independent NIH-supported investigator is directly related to the number of years supported on a traineeship or fellowship. Another key recommendation was the modification of the Clinical Investigator Development Award so that a candidate could obtain two years of basic science training, return to complete the last two years of his/her residency and then proceed with three years of a sponsored research experience. It is expected that such flexibility would be appealing to the physician-scientists in their quest for clinical research careers.

We are also planning to establish a mentor award where established distinquished investigators could apply for a supplement for two to three years to support a physician or basic scientist on a research project in the communication sciences.

Mr. Conte. What is being done to implement these suggestions?

Dr. Snow. NIDCD staff are obtaining the required clearances and will prepare information for dissemination to training directors and potential candidates notifying them of the availability of these training initiatives.

INFORMATION CLEARINGHOUSE

Mr. Conte. What is the status on the development of your Institute's information clearinghouse?

Dr. Snow. The NIDCD Clearinghouse is rapidly becoming a reality. We are awaiting final clearances for our Request for Contracts to be issued immediately upon such approvals. We are looking forward to beginning our implementation phase this fiscal year and to introducing all critical elements of the Clearinghouse in an orderly sequence. We are especially grateful for the cooperation of over 50 people who represented other clearinghouses, voluntary agencies, and organizations serving individuals represented by our program areas. These representatives met on October 5, 1989, to make recommendations about the development of our Clearinghouse. Their work has proved invaluable in our planning process.

Mr. Conte. How will the clearinghouse work?

Dr. Snow. The NIDCD Clearinghouse will function as a central Institute resource where results of the latest research and information on all Institute program areas (hearing, balance, smell, taste, voice, speech and language) will be made available to patients, scientists, health care professionals, organizations, industry, and the public. The Clearinghouse will respond to routine information inquiries, maintain mailing lists and, in

cooperation with the NIDCD information staff, develop fact sheets, bibliographies, brochures and produce materials for general educational outreach.

Mr. Conte. There was a meeting last October to look at ways to create the clearinghouse -- what were the major recommendations?

Dr. Snow. Recommendations from the meeting participants included creating a plan for computer networking to and from existing databases, ensuring appropriate language levels and complexity for various audiences, screening existing materials to confirm non-duplication of effort, development of an aggressive public relations campaign to publicize the Clearinghouse services and a recommendation that no fee be charged for access to information. We were able to take advantage of many recommendations in the development of the Clearinghouse proposal. We plan to return to these groups for advice as we identify material for use, duplication or referral.

NEUROFIBROMATOSIS

Mr. Conte. Can you tell us about your research efforts involving neurofibromatosis and hearing?

Dr. Snow. The Intramural Audiology Unit has worked collaboratively with several institutes to understand and describe the human hearing system in these complex disorders. This collaborative effort updated the clinical correlates in both known forms of neurofibromatosis (NF). It is a major breakthrough for patient care management in that it is now recommended that wherever possible, complete hearing studies for children and adults with or at-risk for NF1 be included in their diagnostic evaluation and follow-up care. It also represents the first time in the recent clinical literature that NF2 patients have been studied separately from patients with NF1 or from the other, non-inherited form of acoustic tumor. Thus, these data on NF2 provide a clearer picture of the true workings of the auditory system than was previously held. Auditory function is a very dynamic process and regular re-evaluation of auditory function may prove very helpful in management of the illness itself as well as in improving quality of life for patients and/or family members.

Mr. Conte. What efforts are being made to increase N.F. research at your Institute?

Dr. Snow. The Clinical Audiology Unit continues to work with NCI, NINDS, and NICHD in studying children and adults with either NF1 or NF2. We hope to learn still more about the clinical manifestations of these diseases in both affected and at-risk individuals and to correlate our audiological profiles with other clinical studies such as vision, imaging, and genetics markers. We see audiology as a bridge between the laboratory and the patient in helping to define the clinical manifestations of the disease, and of equal importance, to provide improved insights for better patient care management in both genetically-distinct forms of NF.

The Institute is also in the beginning stages of co-sponsorship of a Consensus Conference on acoustic neurinomas.

Following that effort, it is hoped that researchers in various basic and applied sciences across the country will be stimulated to study NF2 from the perspective of its effects on human communication, including hearing, balance, voice, speech, language, smell and taste.

Mr. Conte. How does NF1 differ from NF2 in the ways it affects the hearing system?

Dr. Snow. The singular and most important difference between the auditory system pathology in NF1 and NF2 is that in NF1 acoustic tumors do not occur. The hallmark of NF2 is the presence of bilateral acoustic tumors.

NOISE EXPOSURE

Mr. Conte. Noise pollution is a major occupational hazard for millions of people. Your institute recently held a major conference on this problem. Can you tell us what the conference recommended to reduce noise-related hearing loss?

Dr. Snow. The panel of experts who participated in the NIH/NIDCD Noise and Hearing Loss Consensus Conference reported that exposure to loud sounds in the work place or in recreational activities can produce irreversible and untreatable hearing damage. The panel called for a broadening and vigorous enforcement of existing noise control in the work place and of product noise labelling information for consumers. Another significant recommendation was for public education. Our Institute will be addressing both work place dangers and high-risk groups of children as targets for prevention messages as part of an ongoing public education campaign.

CLEFT LIP AND PALATE

Mr. Conte. We heard testimony from Dr. Löe of the Dental Institute on the progress they are making in cleft lip and palate, a major cause of speech difficulty for many children. Are you doing work in this field as well?

Dr. Snow. The NIDCD shares an interest in the topic and is supporting research in this area. For example, work is beginning which will address speech sound development in young cleft palate children. This work will not only document the normal course of development but also identify factors associated with the development of undesirable articulation patterns. Another example of NIDCD-supported research in cleft lip and palate is a project focused on the relationship between preoperative and long-term postoperative anatomic, physiologic, and perceptual measurements in association with surgery to establish velopharyngeal competence for speech. Inadequate velopharyngeal functioning may result in hypernasality (that is, excessive nasality with often accompanying nasal emission of air), a frequent problem for cleft palate speakers. This study will identify variables associated with surgical success.

Mr. Conte. Do you see an opportunity to combine forces with the Dental Institute on this problem?

Dr. Snow. By mutual agreement the two Institutes are dealing with different but equally important aspects of the problem of cleft lip and palate and their associated speech difficulties. Informal liaison between the Institutes has accomplished much in ensuring that this important problem be addressed efficiently.

NERVE REGENERATION

Mr. Conte. Doctor, what progress is being made in nerve regeneration?

Dr. Snow. Two important advances have been made in studies of regeneration of sensory elements in the inner ear following noise- or drug-induced hearing loss. First, NIDCD scientists have demonstrated in birds that the regenerated hair cells are functional, that they establish connections with the brain, and that they restore hearing. Second, and perhaps more importantly, the progenitor cells--those that give rise to the regenerated hair cell--have been identified in birds; these cells have direct homologues in mammals, leading to the hope that similar regenerative activity can be stimulated in mammals and ultimately in humans. Recent results indicate that stem cells in the olfactory neuroepithelium not only generate new olfactory neurons but generate additional nerve or nerve-like cells that migrate to the olfactory bulb of the brain. Studies are underway to determine the structural and functional characteristics of these migrating cells and their final destinations in the brain.

Mr. Conte. What are the applications of this research in other medical sciences?

Dr. Snow. The potential applications of this type of research are far-reaching. Scientists - and science fiction writers - have dreamed of the time when damaged body organs could repair or even replace themselves. Now that functionality of regenerated neural tissue has been established and progenitor cell types identified, common denominators at the molecular level may be discovered that could lead to regeneration of other structures such as the retina of the eye, or even damaged or defective body organs. The olfactory neuroepithelium may be a source of additional cells for nonolfactory regions of the brain; the olfactory neuroepithelium may prove to be useful in replacing damaged brain cells with new brain cells.

MOLECULAR GENETICS RESEARCH

Mr. Conte. What are the prospects for molecular genetics research in looking at ways to prevent and perhaps treat childhood deafness?

Dr. Snow. The molecular biological approach to the determination of the precise causes of genetically-related sensorineural deafness in children offers the greatest possibility of ultimately finding effective methods of prevention and treatment. Progress will be slow in identifying the responible DNA, but the goal is believed to be attainable.

Mr. Conte. Are you working with the new genome center to share information?

Dr. Snow. The approach of the new Genome Center to the understanding of genetically-related health disorders in humans is the converse of that adopted by the NIDCD Laboratory of Molecular Genetics. The former starts with normal human DNA and seeks to determine the function for which each base pair is responsible; the NIDCD Laboratory starts with deaf subjects and seeks to identify the DNA responsible for the abnormality. The two quite different approaches are complementary to each other but must be implemented separately at present; they will eventually come together.

OTOSCLEROSIS

Mr. Conte. As you know, Doctor, otosclerosis is the most common cause of progressive conductive hearing loss in the adult with a normal eardrum. What progress is being made in otosclerosis?

Dr. Snow. Although otosclerosis has been recognized as a familial disease for many years, the search for its exact mechanisms continues. Recent research has found viral antigens in otosclerotic bony overgrowth, suggesting that unidentified viruses may play a role in triggering its onset. Other studies of otosclerotic patients have found abnormally low levels of messenger-RNA for certain enzymes involved in the synthesis of collagen, a connective tissue. Thus, it is possible that some persons could be unusually susceptible to viral activity that results in otosclerosis. An NIDCD-supported physician-scientist has found that a class of drugs, bisphosphonates, act effectively to inhibit bone remodeling. Two of these drugs (one already FDA-licensed) are nearly ready for clinical trials; if shown to be effective they could be used to prevent the onset of otosclerosis in members of families known to be prone to the disease or to arrest the progress of the disease in persons already affected.

Mr. Conte. What progress is being made in developing substitute bones for the middle ear?

Dr. Snow. The tiny, delicate bones of the middle ear (the auditory ossicles) may be irreparably damaged by chronic ear infections or, less commonly, by trauma, such as nearby explosions or blows to the head. Three ways of replacing the ossicles are now available, in the form of homografts, autografts, or prosthetic devices made of plastic or ceramic. A homograft is donor tissue: ossicles donated by another person, in the familiar tradition of heart, cornea, and kidney transplants. An autograft involves fashioning a substitute ossicle from a person's own body tissue, such as a tooth or a segment of bone from another part of the body. Both homografts and autografts have been used by ear surgeons for a number of years. Prosthetic devices made of plastics such as teflon, silastic, or hydroxyapetite, and new lightweight ceramic materials are used quite successfully as non-organic replacements for the middle ear ossicles, as well.

DRUGS TOXIC TO HEARING

Mr. Conte. There are many, many drugs which have the potential to cause damage to hearing. What research is underway in looking at ototoxic drugs?

Dr. Snow. Research is currently focused in two areas: First, identification of drugs that minimize, eliminate, or protect against ototoxicity; and second, defining mechanisms that underlie the toxic effects of certain drugs on the ear. A significant advance has been achieved in the identification of an antibiotic, fosfomycin, which (preliminary evidence suggests) is effective in protecting against the ototoxic effects of cisplatinum, a cancer treatment drug, and the aminoglycoside antibiotics such as gentamicin and kanamycin. Chronic bacterial infection with drainage from the middle ear is often caused by an organism most effectively treated with drops containing an aminoglycoside antibiotic, that are applied directly to the middle ear. Because of the proximity of the middle and inner ears, some physicians feel that application of those drops carries a risk of inducing permanant inner ear damage. Now a new drug, ciprofloxacin, has been shown to be effective against that bacterial organism, yet can be taken by mouth by patients who are able to swallow, thus avoiding the risk of ototoxicity.

Recent NIDCD research has shown that the risk of ototoxicity in patients increases significantly with increasing age. That is, older patients will develop drug-induced hearing loss more readily than younger patients given the same dosage level of the same drug. This finding has serious implications in the medical care of older persons, who are more likely to take drugs known to be toxic, such as Lasix (furosemide). The action of enzymes in the middle ear necessary for cell growth and differentiation can be blocked by gentamicin, an aminoglycoside antibiotic often given to infants in intensive care nurseries to protect them against life-threatening infections. With the well-known interaction of such drugs with noise, infants are placed at very high risk of developing permanent hearing loss. Studies are now in progress to determine whether hair cells damaged as a result of ototoxic drugs can be stimulated to regenerate in mammals.

Mr. Conte. Do you work with the FDA in finding ways to decrease drug-related hearing loss?

Dr. Snow. The FDA is concerned with evaluating the efficacy and safety of drugs and devices prior to approving their use in humans. NIDCD supports clinical trials of some drugs, but it is also concerned with examining the physiological and pharmacologic mechanisms that underlie the efficacy as well as the toxicity of drugs. Once those mechanisms have been defined, further research can lead to ways in which toxic side effects can be minimized or eliminated and that information can then be used to develop new, safer, and more effective drugs.

SUDDEN DEAFNESS

Mr. Conte. Sudden, acute deafness strikes one out of 5,000 Americans each year. What is known about this disorder?

Dr. Snow. Sudden acute deafness strikes an estimated one out of 5,000 Americans each year. The onset of hearing loss is accompanied by tinnitus (ringing in the ear) in about 98% of all cases, and frequently by acute dizziness as well. The disorder usually affects only one ear and may be due to: a) vascular problems, such as interruption of the blood supply to the inner ear; b) a viral attack on the inner ear, usually associated with a respiratory infection; c) a break in the membranes of the inner ear, which can be caused by sudden pressure changes; or d) autoimmune disease or reactions. In most cases, however, the cause of the sudden deafness cannot be determined and it is classified as idiopathic. Multiple treatment approaches are used, including vasodilators and steroids, but since the cause of the episode is usually unknown, selection of an appropriate treatment becomes quite empirical. There is currently no consistent standard of treatment, nor any way of differentiating among the various underlying causes on the basis of symptoms or test results. There is recovery of function in about 65% of affected persons, either spontaneously or through the use of the drug treatment. The remaining persons are left with permanent hearing loss and tinnitus, often so severe that a hearing aid is of no use.

Mr. Conte. What should be done in research?

Dr. Snow. Perhaps the most important research need is to develop a more detailed perspective on the mechanisms underlying sudden onset of deafness, including studies of the temporal bones of individuals known to have suffered sudden deafness. More sensitive diagnostic tests should be developed that allow differentiation of viral, vascular, autoimmune, and mechanical (membrane breaks) sources of sudden deafness so that appropriate treatment can be instituted. Controlled clinical trials are needed to assess the efficacy of new drugs, including some anti-viral drugs. However, evaluating drug efficacy will be complicated by the high rate of spontaneous recovery known to be typical of the disorder. Epidemiological studies of the incidence of the disorder could help to identify persons at risk for sudden deafness.

EPIDEMIOLOGY

Mr. Conte. I understand your institute has a strong need to develop a program in looking at the distribution of speech and hearing disorders. Can you tell us how such studies might help?

Dr. Snow. Epidemiological information regarding the prevalence of the comunication disorders within the purview of this Institute is greatly needed. Such information will be used by this Institute to guide program planning, establish research priorities, and communicate information of vital use to the lay and professional communities, in their identification of and service to those with communication disorders.

SPACE REQUIREMENTS

Mr. Conte. Is there adequate space for your intramural research program?

Dr. Snow. NIH and the Institute have recently negotiated additional space for the intramural program in the amount of approximately 5,300 square feet.

Mr. Conte. Are you satisfied with the efforts so far?

Dr. Snow. These arrangements will be satisfactory for the current intramural research programs as well as new activities that we will initiate.

OTITIS MEDIA

Mr. Conte. Do you think that vaccines for otitis media are possible?

Dr. Snow. Definitely. Clinical studies have identified the most common bacterial and viral strains associated with otitis media; bacteriological studies have described the physical characteristics of the organisms; and new developments in molecular biology have improved the technologies available for developing vaccines. Thus, we know the identity of the responsible infectious agents, know how they are "constructed," and have the tools available to design vaccines uniquely suited for the bacterial characteristics. Those are essential first steps.

Mr. Conte. What are some of the obstacles you face in developing a potential vaccine for otitis media?

Dr. Snow. Several challenges clearly exist in planning for vaccine development, although these challenges need not be viewed as obstacles: First, developing vaccines that provide protection for children at a very early age when they are most susceptible to the development of otitis media. Currently, it is difficult to provide protection for infants under 18-24 months of age. Second, the appropriateness of the animal models currently used for this research need to be demonstrated; that is, are the findings in animals directly transferable to humans? Third, more information is needed on viral-bacterial interactions in the development of otitis media; there is some evidence that viruses play a significant role in bacterial otitis media. Fourth, the contribution of individual immunological and genetic characteristics to susceptibility to vaccines is not clearly understood, and future clinical trials would have to take those factors into account when evaluating vaccine efficacy.

PHOTODYNAMIC THERAPY

Mr. Conte. What is photodynamic therapy?

Dr. Snow. Photodynamic therapy is an approach utilizing two photosensitizing dyes activated by red laser to treat recurrent respiratory papillomatosis. This procedure in effect is a surgical one, but does not result in scarring, a frequent and often severe result of traditional surgical treatment of the disorder.

Mr. Conte. How are you using this new technology?

Dr. Snow. Researchers are exploring the use of photodynamic therapy in the treatment of papillomavirus infections of the larynx and upper respiratory tract. These infections cause a serious and potentially life threatening disease which affects both children and adults. Photodynamic therapy has been found to be a viable and usable modality of treating upper respiratory tract recurrent papillomatosis. Initial animal study results have shown that the clinical disease can be eliminated, as well as eliminating the presence of the viral DNA in the treated tissue. This represents a new approach to the treatment of this difficult and frustrating disease.

SPACE

Mr. Stokes. Last year, we heard a lot of concern about the lack of space for this new institute. Do you feel that your space needs have been met?

Dr. Snow. Additional space for the Extramural Program will be available in May 1990 in the Executive Plaza Building. Approximately 4,000 square feet have been assigned. Also in May 1990, the Director's office and his immediate staff will occupy 3,000 square feet in Building 31. Both of these units will move into slightly larger space in 1991. We also plan to occupy additional space for the intramural program which will collocate our clinical research units and provide room for expansion. These increments are adequate to meet our mission.

NIDCD GOALS

Mr. Early. Last year, Dr. Moskowitz identified short-term goals for your new Institute. What progress have you been able to make within the past year in achieving these goals?

Dr. Snow. Dr. Moskowitz identified five short-term goals for the NIDCD. I can report to you that progress has been made in each of these.

(1) Applying cellular and molecular biology and genetics: The time is ripe in biomedical research to exploit the latest technology and apply these techniques to studies of communication disorders which are clearly hereditary. The gene for Usher's syndrome which causes deafness and blindness has been found. We are looking for the gene for Waardenburg's syndrome.

(2) Training and career development: This remains a high priority for the NIDCD. This year we have a better focus on this issue as the result of a Workshop we held in July 1989. The outcome was a plan for training for the NIDCD and many of the recommendations from this meeting have been initiated.

(3) Epidemiology studies: There remains a critical need to determine the incidence and prevalence of the many diseases and disorders within the program areas of the NIDCD. We intend to develop an Epidemiology Section within the Office of the Director to address the most effective ways to obtain epidemiologic data, from both existing and new sources of information.

(4) Multipurpose Centers: These centers were legislatively mandated by the Congress in the legislation that established the NIDCD. The Institute issued a Request for Applications in December 1989. We expect to award three to five centers in FY 1990.

(5) Information Clearinghouse: This was another legislative mandate of the new Institute. We have undertaken a number of activities related to the development of this national information Clearinghouse. Substantial progress has been made in our plans for this activity and we expect to issue a Request for Contracts for the Clearinghouse in FY 1990.

LONG-RANGE RESEARCH PLAN

Mr. Early. Has NIDCD, in conjunction with its National Advisory Board and Council, established a long-range plan for research on deafness and communication disorders? If so, would you summarize the recommendations of this plan?

Dr. Snow. The Institute has developed a long-range plan, the National Strategic Research Plan and has recently developed a process by which two of the six scientific areas covered under the Plan will be reviewed and revised every year. This approach will allow for a full examination of the National Strategic Research

Plan every three years, assuring that, at any particular time, no part of the Plan is more than three years old.

The National Deafness and Other Communication Disorders Advisory Board will participate in this process by establishing two committees to review the research plans for two of the Institute's six scientific areas. The Advisory Board's committees will recommend individuals who might serve on panels to revise the Plan, will suggest appropriate levels of Institute activity in these areas, and will suggest initiatives the Institute might undertake. The National Deafness and Other Communication Disorders Advisory Council will participate in the development of the long-range plan, through its Research Committee, which will identify and propose new Institute initiatives for Council review and approval. Once the Board and Council have developed their recommendations, these will be forwarded to the Plan's research panels for their consideration in revising the Plan.

RESEARCH PROJECT GRANTS

Mr. Early. How many new and competing grants will be funded under the Budget Request, and how does this compare with FY 90 and FY 89?

Dr. Snow. We will fund 102 competing research project grants in FY 1991. In FY 1989, we funded 97 grants and in FY 1990, the Institute will fund 113 competing grants.

Mr. Early. What are the payline percentiles? Can you give us some idea of what these mean in terms of priority scores?

Dr. Snow. The payline percentile for FY 1991 will be approximately 25 and the priority scores would be in the 150 to 160 range.

Mr. Early. What about the award rate?

Dr. Snow. In the FY 1991 budget request, the award rate will be approximately 33%.

Mr. Early. To what extent will there be a downward negotiations in competing and noncompeting grants under the budget request?

Dr. Snow. Downward negotiations for competing research project grants will be 8.0% and the noncompeting will be 9.0%.

ATTRACTING RESEARCHERS

Mr. Early. Since NIDCD is a new Institute, what effect do you think this will have on attracting researchers to fields important to the Institute?

Dr. Snow. I am very optimistic that we will be able to recruit very experienced, very able researchers to the NIDCD. We face the same challenges that other Institutes at NIH face in recruiting researchers to both the intramural and the extramural programs. I do believe, however, that we offer a real opportunity

to investigators to study a number of exciting, rewarding research questions. This new Institute is, in my judgment, one of the most attractive enterprises that exists in biomedical research and I believe we will be successful in recruiting researchers.

RESEARCH CENTERS

Mr. Early. The NIDCD plans to establish five new centers in FY 90. Tell us a little more about your plans. What types of centers will be funded? What do you estimate as the average award for these new centers?

Dr. Snow. The National Multipurpose Research and Training Centers were designed for the multi-disciplinary study of communication sciences and disorders. They have as their goals the support of basic and clinical research; research training; continuing education for health professionals; and dissemination of information to the public. These Centers may focus in one or more of the program areas of the Institute, that is, hearing, balance, voice, speech, language, smell and taste. This program has high priority within the NIDCD. The Request for Applications was issued in the NIH Guide to Grants and Contracts in December 1989 and as of January 1990, the Institute had received 85 inquiries regarding submitting an application. We estimate that we may issue three to five awards for an average cost of $1.2 million.

Mr. Early. Please provide for the record a list of the current centers funded by NIDCD.

Mr. Snow. The list of centers currently funded are as follows:

Research Centers
(Currently Active)

	1989 Actual
Mechanisms of Auditory and Vestibular Dysfunction Univ. of Minnesota Medical Center Minneapolis, MN	$1,221,822
Otitis Media Pathogenesis Research Program Univ. of Minnesota Medical Center Minneapolis, MN	1,095,991
Speech Movement Research with an X-Ray Microbeam University of Wisconsin Madison, WI	1,122,374
Chemosensory Clinical Research Center Monell Chemical Senses Center Philadelphia, PA	771,543
Communication Disorders in Children Father Flanagan's Boys' Home Omaha, NE	779,196

Iowa Cochlear Implant Project Univ. of Iowa Iowa City, IA	691,922
Information Processing by the Auditory System Loyola University Chicago, IL	577,065
Experimental and Clinical Studies of Presbycusis Medical Univ. of South Carolina Charleston, SC	703,381
Communication Disorders Clinical Res. Center Univ. of Calif. at Los Angeles Los Angeles, CA	863,837
TOTAL	7,826,231

EXPLORATORY GRANTS PROGRAM

Mr. Early. Your institute plans to initiate a new exploratory grants program. What is the impetus for establishing this new program and what are its goals?

Dr. Snow. Many multi-disciplinary research environments exist in communication sciences; our existing, active centers and program projects are able to organize a research and training center and prepare a competitive application. The Exploratory Grant Program is an innovative mechanism to allow other institutions with potential to develop so that they can to respond to subsequent announcements for the Multipurpose Research and Training Centers.

Mr. Early. How will it work? What is the timetable for awards? How much are you allocating for this program?

Dr. Snow. This exploratory grants program will enable institutions with limited experience in setting up multi-disciplinary research programs an opportunity to develop such a program and test it. The awarding of an Exploratory Grant will allow the development and strengthening of the research program of the institution, and may enable that institution to compete for a multipurpose center. We are requesting $747,000 for the exploratory grant program in FY 1991.

Mr. Early. How much is included in your FY 91 request for this new initiative? Is this "new" money, or are you reallocating funds from other activities?

Dr. Snow. Three exploratory centers at a cost of $747,000 are included in the FY 1991 request. This represents a reallocation of funds within the NIDCD's budget.

RESEARCH TRAINING

Mr. Early. Your statement indicates that a panel of experts was convened to identify critical research training activities to be implemented. Would you briefly summarize the panel's findings.

Dr. Snow. The training panel emphasized that new investigators must be trained and established investigators who are currently engaged in research in related areas must be encouraged to bring their skills and expertise to the studies of the communication sciences and disorders. The panel made a number of innovative suggestions for tackling this challenging issue of research training, among which are the mentor award programs, Physician Scientist Awards, and intensive seminar programs in NIDCD-supported research laboratories. Special emphasis will be placed on targeting underrepresented minorities and communicatively-impaired individuals.

Mr. Early. What recommendations were made for the next year or two, and to what extent does your budget request include sufficient funds to implement these recommendations?

Dr. Snow. Some of the recommendations that the Institute plans to implement within the President's Budget request are the following:

1. Increase utilization of short-term (T35) training program on Institutional NRSAs.
2. Initiate small grant (R03) program for pilot and high-risk research projects.
3. Create a mentor award program by providing supplements to current R01 awardees for two to three years of training of quality candidates.
4. Publication of brochures describing all training and career development mechanisms supported by NIDCD for distribution at professional meetings.

Mr. Early. Last year, we were told that an area of serious concern was predoctoral trainees. What steps is NIDCD taking to address this issue? How does your budget request address this issue?

Dr. Snow. The Institute will place greater emphasis on supporting predoctoral programs through the Institutional National Research Service Award. We will continue the use of conference grants to encourage potential trainees to attend professional meetings and to observe the exciting opportunities available in research careers in the communication sciences. We are making plans for intensive seminar programs within the laboratories of the Institute-supported researchers.

INTRAMURAL RECRUITMENT

Mr. Early. Is the Institute still having difficulties in recruiting certain specialists, such as otolaryngologists, for the intramural program? Has the situation improved any?

Dr. Snow. We are experiencing the same problem as the other institutes at NIH in our retention and recruitment of experienced research scientists. This seems to be primarily due to NIH's inability to offer competitive salaries and the limited portability of benefits. In general, senior NIH physicians are paid 50 percent less than their academic counterparts.

CLINICAL TRIALS

Mr. Early. Does the Budget request include funds for any new clinical trials in FY 91?

Dr. Snow. The FY 1991 budget request does not have funds for new clinical trials.

Mr. Early. Are there any high priority clinical trials which are ready but cannot be initiated because of lack of funds in the FY 91 Budget Request? If so, please provide a list of these, along with a brief description and the associated costs, including first year cost.

Dr. Snow. We do have a list of clinical trials to begin in FY 1991 if funds were available. The list is as follows:

MAJOR NEW CLINICAL TRIALS TO BEGIN IF FUNDS WERE AVAILABLE
(Dollars in thousands)

	First Year Cost	Total Projected Cost
Evaluation of Thyroplasty for Treating Vocal Fold Movement Disorder	$100	$500
Drug Treatment of Tinnitus	1,500	7,500
Prevention of Central Auditory Changes Following Peripheral Hearing Impairment	300	600
Use of Steriods and Surgery for Treatment of Olfactory Defects	800	4,000
Intraoperative Cranial Nerve Monitoring as a Means of Preventing Sensory Deficits Following Neurosurgery	500	1,500
Total	3,500	14,700

RESEARCH CAREER PROGRAM

Mr. Early. Bring us up to date on the Institute's research career program. What types of awards have been established and what areas of need are being addressed.

Dr. Snow. We are planning to fund 44 awards in the Research Career program in FY 1991. As recommended by the panel on training last summer, we plan to start utilizing the Physician Scientist Award to help train and support newly-trained clinicians for development of independent research skills and experience in a fundamental science within the framework of an interdisciplinary research and development program.

INTRAMURAL PROGRAM

Mr. Early. What progress has been made in the past year in strengthening the intramural program, and what are your plans for FY 91?

Dr. Snow. In the past year, we have added additional staff to our Intramural Program, and we are in the process of recruiting a Director for this critical function. We now have very strong basic science research as well as strong programs in speech and voice, as well as audiology. In fiscal year 1991, we will continue these efforts, especially in Waardenburg's Syndrome, hair cell motility, speech disorders, and voice tremors.

Mr. Early. Has NIDCD been allocated sufficient space for its intramural laboratories and clinics? What about for the management of your extramural programs?

Dr. Snow. NIH has allocated additional space for both the intramural and extramural research programs. This space will permit the Institute to consolidate its current activities as well as its new initiatives. If the relocation proceeds as planned, the new arrangements will be quite satisfactory.

Mr. Early. I understand that the Institute will develop a Laboratory of Molecular Genetics. What is the status of this initiative? Are funds sufficient included in your FY 91 request for this purpose?

Dr. Snow. The Institute has plans to establish a Laboratory of Molecular Genetics and pursue research programs in molecular biology and genetics in the areas of hearing and balance as well as voice, speech, language and the chemosenses. In fiscal year 1991, we may be able to hire one or two staff to begin this particular initiative.

EPIDEMIOLOGY SECTION

Mr. Early. You also plan to establish an epidemiology section. Why is this important and what is the status of this initiative?

Dr. Snow. There is a need to establish an epidemiology section to pursue demographic and population-based studies in order to specify the incidence and prevalence of various communication impairments. It is difficult to assess, with current information, the actual numbers of individuals who experience problems of hearing, balance, speech, voice, language, smell and taste. It is also important to understand the factors which may be associated with these impairments. The Institute is planning to initiate an epidemiology section in fiscal year 1991, and we will continue the population-based study of speech and language disorders which will be funded by contract in 1990.

Mr. Early. Are sufficient funds included in the budget request for this purpose?

Dr. Snow. There are funds in the FY 1991 budget request to start an epidemiology unit.

USE OF ADDITIONAL FUNDS

Mr. Early. If an increase over the FY 91 request is provided, how would you use this additional funds?

Dr. Snow. I would, first, increase the number of individual and institutional training grants funded. Secondly, I would increase the number of centers funded by the Institute, in both comprehensive centers and in the new exploratory centers. Ideally, if additional funds were available, I would increase the number of research project grants funded and reduce the downward negotiation rates in both competing and noncompeting grants. In our Intramural Research Program, I would provide additional funding for the Laboratory of Molecular Genetics. Additional funds would also permit additional contracts and enable the Institute to expand the clinical trials program.

PROFESSIONAL JUDGMENT BUDGET

Mr. Early. Did the Institute prepare a professional judgment budget? What level of funding was called for? How does the professional judgement budget differ from the request before us?

Dr. Snow. We have a FY 1991 professional judgment budget of $161,632,000. This represents a increase of $38,785,000 over the FY 1991 budget request.

Mr. Dwyer. Exposure to loud and continuous noise represents the most common preventable cause of hearing loss. Does the Institute plan any collaborative efforts with OSHA to help alert and train workers and their employers to the dangers of hearing loss in the workplace?

Dr. Snow. Our Institute will be cooperating with all appropriate agencies on an ongoing public education campaign aimed at high risk groups that would include persons who work with heavy machinery or whose work exposes them to specific noise dangers. The Institute is deeply committed to reaching both employers and employees with these prevention messages. We are well aware that minority workers are at special risk for noise-induced hearing loss as they tend to occupy positions in trades which traditionally have noisy environments.

Mr. Dwyer. Do you believe that a more energetic effort to promote ear protection in the workplace would reduce the number of hearing loss cases?

Dr. Snow. Exposure to loud sounds in the work place can produce irreversible and, to our current knowledge, untreatable hearing damage. This damage is fully preventable. We believe that public education, business owner and supervisor education, as well as education for the worker about how to protect himself/herself is of critical importance. Our recent consensus conference panel on noise also called for a broadening and vigorous enforcement of existing noise control regulations in the work place.

Mr. Dwyer. What clinical research efforts are underway to help individuals who have lost or damaged their hearing because of workplace noise?

Dr. Snow. NIDCD currently supports a program project in rehabilitation dealing with improving methods of speech reading, improving speech understanding with sensorineural hearing loss and preserving intelligibility with long standing neural hearing loss. This project could have significance for individuals who have sustained or acquired sensorineural hearing loss due to noise in the work place.

Mr. Dwyer. As more women enter nontraditional occupations, such as construction and factory work, has the number of hearing loss cases also increased? Are there any ongoing studies to compare the rate of workplace noise induced hearing loss between men and women?

Dr. Snow. Between the ages of 10 and 20, young men begin to exhibit poorer hearing than do women, a phenomenon that continues well into advanced age. The noise consensus conference panel said that this observation is attributable to the likelihood that men have had greater exposure to noise. From this, we might conclude that a demographic study will be needed to address fully this question. However, the Institute is currently providing partial support to a six-year long nationwide survey by the National Center for Health Statistics study "National Health and Nutrition

Examination Survey" looking at hearing levels from perspectives including location of workplace, kind of work and gender of worker. We are hopeful that the results of this effort will yield the information we need to make appropriate predictions about the long term effects of noise in the workplace.

TRAINING

Mr. Weber. Isn't training of critical importance? Would pre-doctorates and post-doctorates be attracted to the field if they thought more money was available to support them?

Dr. Snow. Training is of critical importance. It is the foundation upon which excellence in research is built. More candidates at both levels would be attracted if they thought more funds were available to support them.

GENETICS

Mr. Weber. What opportunities are there for research in the genetics of hearing loss and other communication disorders?

Dr. Snow. There are great opportunities available to researchers studying the genetics of hearing and other communication disorders. Advances made in our understanding of the nature and causes of genetic disorders will allow early diagnosis, treatment, and counseling, including early education and patient and family training. for affected families. As an example of this research, our scientists are committed to identifying the genes and their products responsible for hereditary deafness. This research holds the promise of genetic replacement and interrupting the aberrant process to prevent deafness.

EPIDEMIOLOGY

Mr. Weber. I understand you have little or no research in epidemiology. How can this be improved?

Dr. Snow. The need for sound epidemiologic data exists in all areas within the NIDCD mission. The Institute will address this need by establishing an Epidemiology Section. This Section will utilize the extensive data base that already exists to obtain a current estimate of the incidence, prevalence, and risk factors for both genetic and acquired deafness and hearing impairment. This Epidemiology Section will also initiate studies of disorders of voice, speech, language, vestibular function, and the chemical senses.

CENTERS

Mr. Weber. What could be done if more money were available for centers?

Dr. Snow. If additional funds were available, I would use them to fund more National Multipurpose Research and Training Centers which support basic and clinical research, research training, continuing professional education and dissemination of information to the public. Ideally, the institute would support one or two of these centers in each of the major program areas of the institute.

STAFFING

Mr. Weber. What is your estimate of your need for increased staffing?

Dr. Snow. A strong foundation was established under Dr. Moskowitz's able leadership. Excellent extramural and intramural scientific programs were transferred from the Neurology Institute and very able individuals have been hired in the administrative areas. I will be recruiting a number of key, senior level positions over the next few months, including the Clinical Director, Scientific Director, the Director of the Division of Extramural Activities, and the Executive Officer. We also need to recruit staff for a Laboratory of Molecular Genetics and an Epidemiology section.

SPACE

Mr. Weber. Are steps being taken to assure that the new Institute has adequate space? Are you satisfied with these efforts to date?

Dr. Snow. The NIH and the NIDCD have recently negotiated additional space for our Intramural Program, our Extramural Program and the Office of the Director and his immediate staff. I believe that these arrangements will be satisfactory for the current program and will accommodate new activities that we intend to initiate.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

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NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

For carrying out section 301 and title IV of the Public Health Service Act with respect to deafness and other communication disorders, [$119,000,000] *$122,847,000*

(Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 1990.)

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Amounts Available for Obligation 1/

	1989 Actual	1990 Appropriation	1991 Estimate
Appropriation.....	---	$119,000,000	$122,847,000
Enacted administrative reduction.....	-1,070,000	-161,000	---
Sequester order.....	---	-1,256,000	---
Subtotal, adjusted appropriation.....	-1,070,000	117,583,000	122,847,000
Real transfer from the National Institute of Neurological Disorders and Stroke.....	95,432,000	---	---
Comparative transfer from: Office of the Director for FTE increase.....	326,000	---	---
Comparative transfer to: Fogarty International Center for passport activities.....	-1,000	-1,000	---
Subtotal, adjusted budget authority.....	94,687,000	117,582,000	122,847,000
Unobligated balance lapsing....	-87,000	---	---
Total, obligations.....	94,600,000	117,582,000	122,847,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1989 -- $460,000; 1990 -- $500,000; 1991 -- $500,000.

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Budget Mechanism
(Dollars in thousands)

	1989 Actual		1990 Appropriation 1/		1991 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Grants						
Research projects:						
Noncompeting.....	314	$57,678	313	$63,936	326	$68,187
Administrative supplemental.....	(4)	260	(3)	747	(3)	755
Competing:						
Renewal.....	41	10,397	48	13,351	42	13,711
New.....	50	5,785	59	7,691	55	8,032
Supplemental.....	6	791	6	754	5	640
Subtotal, competing..	97	16,973	113	21,796	102	22,383
Subtotal, research projects	411	74,911	426	86,479	428	91,325
Research centers:						
Specialized/ Comprehensive centers..	9	7,826	14	13,092	14	13,092
Subtotal, centers...	9	7,826	14	13,092	14	13,092
Other Research:						
Research career programs.	31	1,943	44	2,856	44	2,856
Minority biomedical research support.....	0	0	(4)	300	(4)	326
Other research related...	7	220	6	327	6	327
Subtotal, other research....	38	2,163	50	3,483	50	3,509
Total, research grants.....	458	84,900	490	103,054	492	107,926

Training						
Individual awards						
Noncompeting.....	7	201	9	218	18	464
Competing:						
Renewal.....	2	59	5	147	6	176
New.....	7	155	18	494	8	219
Subtotal, Individual...	16	415	32	859	32	859
Institutional awards						
Noncompeting.....	67	1,608	68	1,794	68	1,794
Competing:						
Renewal.....	11	244	11	236	11	236
New.....	11	223	11	234	11	234
Subtotal, Institutional....	89	2,075	90	2,264	90	2,264
Total, training.....	105	2,490	122	3,123	122	3,123
Research and development contracts....	6	1,206	5	2,002	5	2,002
	FTEs		FTEs		FTEs	
Intramural research.....	20	2,697	24	4,301	28	4,603
Research management and support.....	17	3,394	38	4,862	42	5,193
Extramural construction....		---		240		---
TOTAL.....	37	94,687	62	117,582	70	122,847
HIV/AIDS.....		(---)		(---)		(578)

1/ Includes approximately $240,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Crosswalk - 1989 Actual

(Dollars in thousands)

	Mechanism								
	Research Grants			Training		Research and Development		Research Management	
	Research Projects	Research Centers	Other Research	Individual	Institutional	Contracts	Intramural Research	and Support	Total
Deafness and Other Communication Disorders	$74,911	$7,826	$2,163	$415	$2,075	$1,206			$88,596
Intramural Research							$2,697		2,697
Research Management and Support								$3,394	3,394
Total	74,911	7,826	2,163	415	2,075	1,206	2,697	3,394	94,687

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Crosswalk - 1990 Appropriation 1/

(Dollars in thousands)

	Mechanism									
	Research Grants			Training		Research and Development Contracts	Intramural Research	Research Management and Support	Extramural Construction	Total
	Research Projects	Research Centers	Other Research	Individual	Institutional					
Deafness and Other Communication Disorders.....	$86,479	$13,092	$3,483	$859	$2,264	$2,002				$108,179
Intramural Research.....							$4,301			4,301
Research Management and Support								$4,862		4,862
Extramural Construction.....									$240	240
Total.....	86,479	13,092	3,483	859	2,264	2,002	4,301	4,862	240	117,582

1/Includes approximately $240,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Crosswalk - 1991 Estimate

(Dollars in thousands)

	Mechanism								
	Research Grants			Training		Research and Development Contracts	Intramural Research	Research Management and Support	Total
	Research Projects	Research Centers	Other Research	Individual	Institutional				
Deafness and Other Communication Disorders	$91,325	$13,092	$3,509	$859	$2,264	$2,002			$113,051
Intramural Research							$4,603		4,603
Research Management and Support								$5,193	5,193
Total	91,325	13,092	3,509	859	2,264	2,002	4,603	5,193	122,847

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National Institutes of Health

National Institute on Deafness and Other Communication Disorders

Summary of Changes

1990 Estimated budget authority	$117,582,000
1991 Estimated budget authority	122,847,000
Net change	+5,265,000

	1990 Current Estimate Base		Change from Base	
	Pos. (FTEs)	Budget Authority	Pos. (FTEs)	Budget Authority
Increases:				
A. Built-in:				
1. Within grade increase		$3,305,000		+$42,000
2. 1991 payraise		3,305,000		+203,000
3. Annualization of January 1990 pay raise		3,305,000		+26,000
4. One extra day of pay		3,305,000		+14,000
5. FTS rate increase		30,000		+1,000
6. Payment for centrally furnished services		1,112,000		+103,000
7. Increased cost of laboratory materials and other supplies		6,130,000		+56,000
8. DHHS Working Capital Fund		44,000		-2,000
Subtotal				+443,000
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	313	64,683,000	+13	+4,259,000
b. Competing	113	21,796,000	-11	+587,000
Total	426	86,479,000	+2	+4,846,000
2. Other research	Pos. (FTEs)	3,483,000	Pos. (FTEs)	+26,000
3. Intramural Research	24	4,301,000	+4	+108,000
4. Research Management and Support	38	4,862,000	+4	+82,000
3. Extramural Construction		240,000		-240,000
Subtotal				+4,822,000
Total changes				+5,265,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Budget Authority by Activity
(Dollars in thousands)

	1989 Actual		1990 1/ Appropriation		1991 Estimate	
	FTEs	Amount	FTEs	Amount	FTEs	Amount
Deafness and Other Communication Disorders.....	---	$88,596	---	$108,179	---	$113,051
Intramural Research.....	20	2,697	24	4,301	28	4,603
Research Management and Support..	17	3,394	38	4,862	42	5,193
Extramural Construction.....		---		240		---
Subtotal, obligations.....	37	94,687	62	117,582	70	122,847
Unobligated balance lapsing.....		87		---		---
Total, Budget Authority.....	37	94,600	62	117,582	70	122,847
HIV/AIDS.....		(---)		(---)		(578)

1/ Includes approximately $240,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Budget Authority by Object

	1990 Appropriation	1991 Estimate	Increase or Decrease
Full-time equivalent of permanent positions	62	70	+8
Total compensable workyears: Full-time equivalent employment	62	70	+8
Average ES salary	$76,400	$79,474	+3,074
Average GM/GS grade	9.5	9.5	---
Average GM/GS salary	33,656	34,835	+1,179
Average salary, grades est. by act of July 1, 1944 (42 USC 207)	70,698	73,172	+2,474
Average salary of ungraded positions	18,929	18,929	---
Personnel Compensation:			
Full-time permanent	2,196,000	2,385,000	+189,000
Other than full-time permanent	364,000	395,000	+31,000
Other personnel compensation	104,000	113,000	+9,000
Special personnel services	192,000	209,000	+17,000
Subtotal, personnel compensation	2,856,000	3,102,000	+246,000
Personnel benefits	449,000	488,000	+39,000
Benefits for former personnel	3,000	3,000	---
Travel and transportation of persons	275,000	286,000	+11,000

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	1990 Appropriation	1991 Estimate	Increase or Decrease
Transportation of things.....	45,000	47,000	+2,000
Rent, communications and utilities...	201,000	209,000	+8,000
Printing and reproduction.....	65,000	68,000	+3,000
Other Services:			
Project contracts.....	2,002,000	2,002,000	---
Centrally furnished services.....	1,112,000	1,206,000	+94,000
Other.....	2,464,000	2,627,000	+163,000
Supplies and materials.....	701,000	729,000	+28,000
Equipment.....	992,000	1,031,000	+39,000
Grants, subsidies and contributions..	106,417,000	111,049,000	+4,632,000
TOTAL.....	117,582,000	122,847,000	+5,265,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Significant Items in House Appropriations Committee Report

Item	Action Taken or To be Taken
1. "The Committee is pleased that the new insitute [NIDCD] has included in its mission a focus on communication disorders in multicultural populations." (page 81)	1. The mission of the NIDCD embraces a broad spectrum of diverse populations. The NIDCD is supporting research on and will expand studies of multi-cultural populations, including the deaf culture and hearing impaired populations.
2. "Currently, only 50 physicians trained in otolaryngology perform research in the U.S. The NIDCD will encourage training of both pre- and post-doctoral candidates on individual and institutional training grants, and in multidisciplinary centers in order to address current and future manpower needs. There are pertinent differences in the prevalence, etiology, and manifestations of speech, language and hearing disorders among minority populations. The NIDCD will encourage the recruitment of minority candidates for research and clinical training to study these areas." (page 81)	2. The NIDCD convened a panel of expert consultants to identify research training activities which could be implemented by the NIDCD in three time periods: the next one to two years, five years from now, and 10 years from now. Twenty-one past, current, and future students, trainees, and fellows shared their views and perceptions of the NIDCD training programs with the panel and with NIDCD staff. Among the recommendations to be implemented as soon as possible were methods for increasing the number of undergraduate college students with knowledge of communication sciences and career opportunities in related biomedical research. Special emphasis will be placed on targeting under-represented minorities and communicatively disabled individuals.

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NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Significant Items in Senate Appropriation Committee Report

Item	Action Taken or To be Taken
1. "Of particular concern to the Committee are the effects of deafness and communicative disorders on children and the aging population. Therefore, the Committee concurs with the NIDCD task force and the Friends of the National Institute on Deafness and Other Communication Disorders, and strongly recommends that the following priority areas receive special attention: one, the continued investigation of genetic factors underlying these disorders, two, new and expanded research training programs for clinicians and other scientists, three, additional clinical trials to determine the effectiveness of drugs, vaccines, and methods of intervention in the prevention or management of certain types of disorders, and four, the expanded development of technology to aid in rehabilitative processes, especially hearing aids, cochlear prostheses, and assistive devices for speech disorders." (page 153)	1. The NIDCD will continue to emphasize these important research areas via the issuance of requests for applications and program announcements. Those in process include: Recognition and Treatment of Perilymphatic Fistulae, National Multipurpose Research and Training Centers, Language learning in deaf children, Treatment efficacy of voice disorders, Neurobiology of taste pathways, Genetics: chemical senses. These solicitations are expected to stimulate additional scientific investigations in these important areas, which will augment the strong science base already supported by the NIDCD intramural and extramural programs.
2. "The Committee is concerned that currently fewer than 50 physicians trained in otolaryngology conduct communication disorders research in the United States, and that too few nonmedical researchers are being trained for work in the communication sciences. In response to this critical need for researchers, the NIDCD will support the research training of both pre- and postdoctoral candidates through institutional and individual training grants and in multi-disciplinary centers. Research career awards will be offered to promote the development of both doctor of philosophy (Ph.D) and doctor of medicine (M.D.) researchers in the scientific areas relevant to the Institute." (page 154)	2. The NIDCD convened a panel of expert consultants to identify research training activities which could be implemented by the NIDCD in three time periods: the next one to two years, five years from now, and 10 years from now. Twenty-one past, current, and future students, trainees, and fellows shared their views and perceptions of the NIDCD training programs with the panel and with NIDCD staff. Among the recommendations to be implemented as soon as possible were methods for increasing the number of undergraduate college students with knowledge of communication sciences and career opportunities in related biomedical research. Special emphasis will be placed on targeting under-represented minorities and communicatively disabled individuals.

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1990 Amount Authorized	1990 Appropriation	1991 Amount Authorized	1991 Budget Estimate
Funded Authorizations:						
Research and Investigation.....	Section 301	42§241	Indefinite	$114,459,000	Indefinite	$119,724,000
National Institute on Deafness and Other Communication Disorders	Section 464 A-F	42§281	Indefinite		Indefinite	
National Research Service Awards.....	Section 487	42§288	Such sums 1/ as necessary	$3,123,000	Authorizing legislation to be requested	$3,123,000
Total Budget Authority				$117,582,000		$122,847,000

1/ This training authority is shared with other research training programs of the National Institutes of Health, and the Alcohol, Drug Abuse and Mental Health Administration.

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NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1989 2/	---	---	$87,600,000	$86,530,000
1990	99,902,000	99,952,000	121,116,000	118,839,000 3/
1990 Sequester				-1,256,000
1991	122,847,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ The House allowance excluded funds for the unauthorized training programs (National Research Service Awards). The Senate allowance includes the budget for NRSA's. It included up to $93,100,000 for establishment of the proposed new National Institute on Deafness and Other Communication Disorders (NIDCD). The appropriation included the budget of the NRSA program and provided up to $96,100,000 for the establishment of the proposed new institute, NIDCD.

3/ Reflects enacted administrative reductions of $161,000.

Justification

National Institute on Deafness and Other Communication Disorders

	1990 Appropriation		1991 Estimate		Increase or Decrease	
	FTEs	BA	FTEs	BA	FTEs	BA
TOTAL.....	62	$117,582,000	70	$122,847,000	+8	+$5,265,000
HIV/AIDS..	(---)	(---)	(1)	(578,000)	(+1)	(+578,000)

General Statement

In October 1988, the National Institute on Deafness and Other Communication Disorders (NIDCD) became the 13th Institute mandated by Congress within the National Institutes of Health. The NIDCD conducts and supports research and training on disorders of hearing and other communication processes, including diseases affecting hearing, balance, voice, speech, language, taste, and smell through a diversity of research performed in its own laboratories, a program of research grants, individual and institutional research training awards, career development awards, center grants, and contracts to public and private research institutions and organizations. The Institute also conducts and supports research and training that is related to disease prevention and health promotion, and the special biomedical and behavioral problems associated with people having communication impairments or disorders. The NIDCD supports efforts to create devices which substitute for lost and impaired sensory and communication functions, and to collect and disseminate information to health professionals, patients, industry, and the public on research findings in these areas.

We live in an age when the tools of communication are extraordinarily sophisticated. The ability to communicate effectively has a major effect on an individual's functioning productively in our society. The NIDCD is striving to maximize the benefits of research advances and to make available the latest technology to Americans who would most benefit from this technology. The Institute will make every effort to ensure that the latest information from research is known to the public, medical professionals, and other scientists.

The NIDCD is pleased to be an active participant in the NIH celebration of the Decade of the Brain. It joins several other Institutes at the NIH in emphasizing research on neurobiology. In addition, research supported by the NIDCD will make significant contributions to research questions in other areas not directly within the Institute's mission. Two examples of these cross-cutting areas are genetics research and neural regeneration research. The advances made in our understanding of the nature and causes of genetic disorders will allow early diagnosis, treatment and counseling, including early education and patient and family training, for affected families. Advances in one area of genetic research contributes to an understanding of all genetic mechanisms. The regeneration of neural tissues after injury and illness occurs in very few places in the human body. The nasal

neuroepithelium is one tissue that does have the ability to regenerate. As scientists supported by the NIDCD strive to unlock the clues to why nasal tissue has this ability, the information they learn can be applied to other nonregenerative tissues.

Overall Budget Policy

The 1991 budget request for the NIDCD is $122,847,000, an increase of $5,265,000 over the 1990 current estimate.

The 1991 budget request for research project grants is $91,325,000, an increase of $4,846,000 over the 1990 estimate. The total number of research grants awarded in 1991 will be 428, as compared to 426 in 1990. The request will support 102 competing research project grants at an average cost $219,441. The request will support 326 noncompeting research project grants at an average cost of $209,163.

The NIDCD will support 14 research centers in 1991 for $13,092,000, the same level of support as the 1990 current estimate.

Other research grants will total 50 awards in 1991, the same as the 1990 level. An estimated 122 research trainees will be supported under the National Research Service Award program, the same level of support as 1990.

The research and development contract budget of $2,002,000 will support five contracts, the same number as 1990.

The 1991 budget request for intramural research is $4,603,000, an increase of $302,000 over the 1990 current estimate. The request for research management and support of $5,193,000, an increase of $331,000 over the 1990 level.

Program Accomplishments

Neurobiology: Studies of mice with normal hearing and those in which partial or total deafness was produced temporarily early in life have demonstrated significant reductions in the number and size of neurons in the cochlear nucleus in the central auditory pathway. This reduction in neurons was greater in those totally deaf than in those with partial hearing. These findings have important implications for the potential consequences of delayed identification and treatment of hearing impairment and deafness in infancy and childhood. Investigators have been pursuing the theory that early hearing loss, even if only temporary, may have long lasting consequences. These consequences can include the inability to use auditory information later in life even if hearing had returned to normal subsequently. Specific auditory deficits may develop if there is incomplete development of the structure of the cochlear nucleus. This research finding provides additional evidence of the critical importance of identifying hearing loss in an infant as early in its life as possible. In an exciting extension of this research, investigators have found that electrical stimulation with a cochlear implant reverses the cell losses in the auditory nerve and brain stem related to early acquired deafness; another group of NIDCD researchers have found that animals with mild to moderate hearing losses did not develop the characteristic auditory nerve or cochlear nucleus changes when treated with hearing aid amplification while the hearing loss existed. These findings underscore the importance of early identification and treatment of hearing impairments in infants and young children, as targeted by the report of the Task Force of the National Strategic Research Plan.

Auditory Hair Cells: Hair cells is another name for auditory sensory cells. NIDCD-supported investigators have established previously that regeneration of hair cells in the cochleas of both young and adult birds occurs spontaneously and can also be induced following ear-damaging drug treatment or traumatic noise exposure. Other researchers have demonstrated that hair cells are replenished in fish almost continuously throughout their life cycle, not following damage. Institute-supported scientists are pursuing this very significant fundamental line of research. The cells that give rise to the regenerated hair cells are being identified and work is in progress to define the biochemical and genetic mechanisms that initiate the regeneration process. Humans do not have the ability to regenerate hair cells. Once cochlear hair cells are lost to trauma or injury, hearing is irreversibly affected. This research has created hope that similar mechanisms can be identified or stimulated in mammals and, ultimately, humans, leading to the ability to reverse acquired hearing loss.

An exciting landmark in auditory physiology was achieved when NIDCD grantees uncovered fundamental information on hair cells of the cochlea. They determined that the hair cells actively oscillate in response to sound and certain biochemical changes, rather than serving as passive mechanical receptors for pressure changes in the inner ear fluids, as had been believed for over a century. This means that hair cells have their own contractile processes and can act like muscles, oscillating in response to nervous system stimulation. This discovery has prompted a re-examination of theories of auditory function and is expected to result in significant advances in solving complex questions about processing of acoustic information.

Tinnitus: Millions of Americans suffer from tinnitus, or a "ringing" in the ears. Researchers in this area have been limited by the lack of a reliable animal model and by the lack of quantitative, objective methods to determine the presence and characteristics of the tinnitus. Studies supported by the NIDCD have resulted in the development of an animal testing technique that enables the detection and characterization of tinnitus, as well as changes in its loudness and pitch. This advance has important implications for evaluation of the effectiveness of different methods of alleviating tinnitus.

New Therapy: Papillomavirus infections of the larynx and upper respiratory tract are a serious disease which affects both children and adults. It can cause a life-threatening obstruction of the respiratory tract. Patients with this infection develop multiple folds that appear as warts. Previously, they were treated by surgical removal. This was not a satisfactory method, however, as scarring often developed. Other conventional and experimental therapies including laser, chemotherapy, vaccines, and interferon have failed to cure this disease. In an exciting advance in this field, a new treatment, an ultraviolet light therapy, has been found to be much more effective for upper respiratory tract recurrent papillomavirus infection, eliminating the need for surgery. Initial animal study results have shown that both the clinical disease and the presence of the viral DNA in the treated tissue can be eliminated. This represents a potentially new and creative therapy for this difficult and frustrating disease.

Identifying Children At-Risk for Speech and Language Disorders: Investigators have uncovered important information in studies of infants at risk for speech and language disorders. Utilizing particular electrophysiologic techniques, they determined that children with abnormal auditory evoked potentials in infancy have specific language deficits at one year. These results suggest that this procedure is effective in identifying at-risk children, as well as indicating that early defects in infants' ability to process auditory information may contribute to impaired development of speech and language function. The significance of this research lies in the early identification of those likely to benefit from the early initiation of treatment.

Language-Impaired Children: A recent study determined that the majority of children who were identified at age 4 as having specific language impairment became severely academically impaired by age 8. Specific language impairment is the term applied to children who are otherwise normal in every measurable respect, but who simply cannot learn language. Language- impaired children were found to experience difficulty with a number of basic skills prerequisite for academic success. Of the various subtypes of language impairments, those language-impaired children who at age 4 had receptive language deficits (the inability to comprehend or understand certain aspects of language) were most likely to have subsequent reading problems at age 8. Results clearly show a developmental continuum between language and reading disorders. Such findings have important clinical as well as research ramifications. Results suggest they represent the same disability which changes its clinical characteristics during development.

Genetics: Researchers are learning more about the basis of language impairment in children through studies of the contribution of genetic factors. Families of language-impaired children were found to be significantly more likely to report a history of impairment in other family members, with higher rates of affected siblings and parents. Although the incidence of language disorders is much greater in boys than girls, family history did not provide support for a sex-linked genetic disorder. A different mode of genetic transmission now appears more likely.

Sign Language: Important strides have been made in our understanding of how deaf children learn sign language. Facial expression functions in distinct ways in American Sign Language (ASL): it conveys emotion and signals certain syntactic constructions. It appears that in the period before deaf children can speak, their emotional abilities serve as a transition mechanism into the facial component of ASL grammar. As the child matures, grammatical facial expressions begin to be acquired at about 2-1/2 years of age. Manually-signed elements of ASL show a developmental priority over facially-marked aspects. These findings provide important information on sign language acquisition in deaf children of deaf parents, and also document the transition from pre-linguistic to linguistic communication.

Language Acquisition: A critical period exists for learning a second language; this ability to learn decreases with age. Results of several studies in normal-hearing and deaf individuals show the effect of age of acquisition on the learning of detailed structures of a second language. This pattern holds true for normal-hearing individuals learning a second language as well as for deaf individuals learning ASL at different ages. Such findings have obvious implications for teaching manual communication to deaf children and indicate the importance of teaching languages as early in a person's life as possible.

Stroke: Recent research has uncovered the value of medical treatment of language problems following stroke in some patients. One complication of stroke in some patients is the loss of the ability to make sense of language. Researchers have determined that this may reflect disruption of specific neurotransmitter systems. Treatment of adults with hesitancy and impaired initiation of speech included use of a dopamine agonist (bromocriptine). Language performance notably improved during this therapy, suggesting that this pharmaceutical agent may be beneficial in treatment of selected symptoms of stroke.

Regeneration of Vestibular Hair Cells: Following the significant discovery that auditory hair cells of birds can regenerate following injury, researchers supported by the NIDCD have focused recently on vestibular hair cell regeneration. It has been determined that the vestibular hair cells of fish are replenished almost continuously throughout the life cycle. The structures and the biochemical and genetic mechanisms involved in this regeneration are actively being studied in the hope that researchers can ultimately learn to restore useful function to human vestibular sense organs that have been traumatized or diseased.

Balance Structures in the Inner Ear: NIDCD-supported scientists have made important advances in understanding the balance structures in the inner ear that sense gravity and linear motion acting on the head. In addition, they

have provided important information on the effect of these structures on the balance mechanisms responding to rotational head movements. These findings have applications for understanding vestibular function in normal and disease states. Researchers have applied these findings to improve the measurement of the adaptive capabilities of those with inner ear vestibular disorders, as well as to plan for more appropriate programs of physical rehabilitation.

New Technology: Researchers have employed the latest computer technology to develop new methods to detect, quantify, and localize the source of vestibular and balance disturbances. Powerful rotational devices now permit the assessment of the capacity of the vestibular system to stabilize vision during the head movements of daily living. Other computer-controlled systems can differentiate the vestibular, visual, and postural contributions to balance and balance disorders. In addition, this technology has assisted in the planning, implementation, and monitoring of rehabilitation programs for individuals with certain vestibular disorders and central nervous system movement disorders.

Nervous System Regeneration: The nasal olfactory neuroepithelium is known to have the remarkable capability to regenerate olfactory receptor neurons from precursor cells throughout life. NIDCD-supported researchers have recently discovered that this neuroepithelium produces another type of cell that migrates into the brain during adult life. Thus, the olfactory neuroepithelium is not only a source of olfactory receptor neurons, which have a powerful nourishing effect on the brain, but also a direct source of additional cells for the brain. Scientists are now identifying the characteristics of these cells, defining the limits of their migration, and studying interactions of cells that normally do not contact each other, as well as the effects of removing certain chemical substances normally present. These findings and approaches have profound implications for the repair and rejuvenation of the nervous system in general by means of regenerative processes and tissue transplantation.

Transplantation: Previous studies have shown that transplants of olfactory neuroepithelial tissue into the brain of young hamsters survived, developed new neurons, and developed neural connections into the brain. In an exciting new extension of this research, results show that olfactory receptor neurons in the neuroepithelial tissue of young hamsters continue to survive, develop, and mature even when the tissue is transplanted into hamsters two years old. These findings have important implications for repair of the nervous system.

National Geographic Survey: Among the five senses, the least amount of epidemiological information has been available for the chemical senses. Recently, a giant epidemiological step was taken in smell. With assistance from NIDCD-supported scientists, the National Geographic Association conducted a massive international smell test and survey. Among the findings were that two of every three respondents reported temporary losses of smell, and those losses often were associated with colds, influenza, sinus conditions, and allergic rhinitus. A disturbing finding was that a substantial segment of the elderly showed a loss in the ordinary negative reaction to the foul-smelling warning agent added to natural gas. Scientists

are analyzing the data base to seek explanations of the results and to evaluate effects such as geographic location and polluted environments on smell perception and sensitivity.

Multipurpose Centers: The legislation that established the NIDCD, Public Law 100-553, mandated that the Institute provide for the development, modernization, and operation of National Multipurpose Research and Training Centers. The Institute anticipates the award of three or four of these multidisciplinary Centers in FY 1990. The goal of these Centers is the support of basic and clinical research, research training, continuing education for health professionals, and dissemination of information to the general public in one or more of the program areas of the Institute. Each of these Centers is a national resource that will utilize multidisciplinary, coordinated approaches to research questions in one or more of the major program areas of the NIDCD: hearing and balance; speech, voice, and/or language; or taste and smell, as well as other disciplines related to these areas.

Research Training and Career Development: The National Strategic Research Plan of the NIDCD recommended that "a first priority of the new institute should be to address this critical shortage of research personnel and training support" by developing an active, long-range master plan for fostering a "community of investigators dedicated to advancing research on human communication and its disorders." A limited number of trainees and fellows are currently receiving support at the predoctoral level in sciences related to hearing, speech, and taste. In July 1989, the NIDCD convened a panel of expert consultants to identify research training activities which could be implemented by the NIDCD in three time periods: the next one to two years, five years from now, and 10 years from now. Twenty-one past, current, and future students, trainees, and fellows shared their views and perceptions of the NIDCD training programs with the panel and with NIDCD staff. Among the recommendations to be implemented as soon as possible were methods for increasing the number of undergraduate college students with knowledge of communication sciences and career opportunities in related biomedical research. Special emphasis will be placed on targeting under-represented minorities and communicatively-disabled individuals.

Intramural Research Program

Laboratory of Molecular Otology: The major purpose of this Laboratory is to conduct research that will give new knowledge of the biological factors affecting hearing. The research conducted in this Laboratory has contributed to a better understanding of how the inner ear translates sound waves into nerve activity and how neurochemical synapses process auditory information originating in the inner ear sensory cells. A long-range goal of the Laboratory is to analyze and describe the auditory sensory organ and the synapses of cells and neurons in the auditory system in terms of molecular biology.

For the past several years, laboratories around the world have been racing to clone one or another of the various types of glutamate receptors present in the brain. These form a class of proteins responsible for excitatory transmission between neurons. Three groups of scientists recently reported cloning sequences of receptors that specifically bind kainate, a well known

glutamate analog. One of these groups is directed by an NIDCD Intramural scientist. For neurobiologists, the cloning of a glutamate receptor or part of a receptor is an exciting event, because glutamate is the main excitatory neurotransmitter in the brain and every neuron known has receptors for glutamate. Intramural scientists will continue their important and promising studies of glutamate receptors. They have already obtained a highly purified preparation from mammalian brain of another type of glutamate receptor, with a high affinity to a compound called AMPA rather than to kainate. The Intramural scientists have shown that these two types of glutamate receptors may be structurally related. They are continuing these very promising lines of research.

An intramural scientist is continuing a study of outer hair cell motility. Outer hair cells are one of two types of hair cells in the mammalian cochlea. The outer hair cell's important role in hearing is to modulate the micro-mechanical properties of the hearing organ. Researchers had previously shown that isolated outer hair cells of the guinea pig cochlea can undergo oscillatory length changes under the influence of an electrical field comparable to the electrical field occurring under normal conditions in the sensory organ of hearing. The Laboratory scientists are continuing these studies, using very sophisticated tools and techniques. These scientists were able to define one of the mechanisms that regulates the movements of the outer hair cell. Experimental support was also found for the theory that calcium ions play an important role in the chain of events leading to the outer hair cell movements.

Speech and Voice Unit: Research in the Speech and Voice Unit is aimed at understanding the nature and causes of speech, voice, and language disorders and developing improved prevention and treatments for these disorders. This year, investigators of the NIDCD intramural program were the first to demonstrate a successful treatment for voice tremor. Voice tremor affects women primarily and makes speech difficult to understand, rendering use of the telephone impossible. Treatments have never before been available for this disorder. Scientists in the speech and voice unit developed a new treatment, injecting botulinum toxin into throat muscles in patients with this disorder, which was very successful in eliminating tremor entirely in some and almost completely in others.

Similar botulinum toxin injections have proven effective in treating another voice disorder, spasmodic dysphonia, which was previously treated by cutting one of the nerves to the larynx. Although the surgery was initially successful, in 60 percent of patients the symptoms usually return within the first 5 years. Studies conducted at the NIH have demonstrated that when symptoms return the muscles of the larynx are reinnervated, either by the nerve growing back or by other nerves. Botulinum toxin injections were effective in reversing the effects of muscle reinnervation and restoring speech.

Clinical Audiology Unit: The Clinical Audiology Unit is involved in numerous multidisciplinary protocols and studies patients from 11 different Institutes at the NIH. One example of its studies is the activities related to both types of neurofibromatosis (NF), types 1 and 2. Audiologic data on NF-1 were presented by staff at an important meeting in April 1989 at the NIH. This meeting underscored the importance of getting data on auditory

system involvement in NF-1 out to the general medical community who are the first medical contact for most patients with NF. Findings from studies conducted by the Clinical Audiology Unit identified abnormal auditory function in these patients. This means that children and adults with or at risk for NF-1 need to be evaluated audiologically on a regular basis and, further, that they may need ongoing audiologic and ear, nose, and throat treatment. These findings are important because type 1 neurofibromatosis is the most commonly inherited neurological disease known to humans and the number of children and adults who have hearing or other auditory system deficiencies may include a substantial percentage of people with NF-1.

Important data have emerged from studies on type 2 NF as well, representing the first time that audiologic data in NF-2 have been reported separately from data on sporadic tumor patients in a modern biomedical study. Findings include the determination that at risk, first degree relatives should be evaluated audiologically on a regular and periodic basis even though hearing loss is not handicapping early in this disease. Audiologic evaluation is a very powerful tool in discovering NF-2, whether or not overt hearing problems are felt to exist. Serial audiologic study is now recommended for patients with, or at risk for, type 2 Neurofibromatosis. These studies are painless, inexpensive, and fast.

Research Management and Support

Information Clearinghouse: The legislation that established the NIDCD mandated the formation of an information Clearinghouse. The purpose of this Clearinghouse is to be an Institute resource where the results of the latest studies funded by the NIDCD could be made available to researchers, professionals, organizations, and other interested individuals. The Institute has undertaken a number of activities toward the development of this organization. It distributed letters to several hundred individuals and groups seeking their guidance on the direction the Clearinghouse should take. Under the auspices of the National Deafness and Other Communications Disorders Advisory Board Subcommittee on the Clearinghouse, a major meeting was held in October 1989 This very successful meeting brought together representatives from many of the major constituent groups of the NIDCD as well as representatives from other Federal Clearinghouses to offer their recommendations and experiences. Three working groups were created at this meeting to address types of information, methodologies for developing and disseminating information, and networking technologies. The report from this meeting was presented to the full Advisory Board at its October meeting. The NIDCD anticipates issuing a Request for Proposals for the information Clearinghouse in FY 1990. The NIDCD is seeking the most efficient means of coordinating the vast amount of information that already exists in the communication disorders field and making information readily available. The Institute's objective is to establish a central resource center that will provide access to current information on an international scale without duplicating existing resources.

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AIDS Research Program

The NIDCD AIDS Program

Clinicians caring for patients with AIDS (HIV positive) or AIDS-related complex (ARC) report that the communication systems of these patients are not spared the ravages of this powerful virus. This is, however, an aspect of AIDS that has not been well documented or researched. The population that is particularly in need of study are the pediatric AIDS patients. These children have shown significant morbidity in communication, hearing, speech, and language. The NIDCD will encourage studies of this very needy and very challenging population.

Recent Research Accomplishments

The NIDCD organized a planning workshop at the NIH in July 1989 with leading experts in the field of AIDS research as it relates to communication disorders. The research questions that need to be addressed were identified and the Institute was given specific recommendations for initiating its AIDS-related research. The NIDCD will begin its support of AIDS research in FY 1991.

Research Plans

Congenital cytomegalovirus (CMV) is a well-established cause of disorders of the auditory, visual, and central nervous systems. Approximately 72,000 children with congenital CMV are born each year, 25 percent of whom will have serious sensory or nervous system disorders. Acquired CMV is recognized as the most common secondary infection among AIDS patients, estimated to occur in more than 90 percent of all such patients. Once acquired, the virus lasts a lifetime and may be completely asymptomatic. Some surveys have established its presence in 50 percent of upper middle class white females and 83 percent of lower class, racial minority women.

New evidence suggests that "quiescent" CMV may actually play a role in the development of Meniere's disease or perilymphatic fistulas. NIDCD researchers have developed a guinea pig model of congenital CMV to determine the ways in which hearing and balance are affected; other studies will focus on CMV in AIDS patients to determine whether the deafness and communication disorders often reported among those patients are due to action of the CMV in an immunocompromised system or to the AIDS virus specifically.

Deafness and Other Communication Disorders

Authorization: Indefinite

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$108,419,000	$113,051,000	+$4,632,000

Purpose and Method of Operation

Hearing/Deafness: More than 28 million Americans are believed to have some degrees of hearing impairment. This estimate includes approximately 2 million persons who are profoundly deaf. One of every 1,000 infants is born totally deaf, and several times this number have a substantial impairment by the age of 3. The most common cause of temporary hearing loss is otitis media, which is predominantly a disease of infants and young children. In a recent survey, this disease accounted for 10 million visits to doctors' offices a year and an unknown number of prescriptions for antibiotics. The estimated health care costs for otitis media in the United States exceed $1 billion per year. At the other end of the age spectrum, more than one-third of the population has a significant hearing impairment by age 65, and the prevalence of age-related hearing impairment (presbyacusis) increases rapidly with increasing age. In years to come these numbers are expected to increase substantially as longevity is extended.

Hearing impairment is invisible and nonfatal, two characteristics that make it attract little public attention. Nevertheless, it is associated with considerable pain and suffering for affected individuals and their families. The NIDCD is striving to stimulate additional research on hearing impairment and deafness and to overcome a long history of societal discomfort and ignorance about deafness.

Rationale for the Budget Request

The 1991 budget request for research project grants is $113,051,000, an increase of $4,632,000 over the 1990 estimate. The total number of research grants awarded in 1991 will be 425, as compared to 426 in 1990. The request includes the support of 14 research centers, 50 Other Research grant awards, 122 research trainees, and the same level of support for research and development contracts as in 1990.

Cochlear Implants: Implantable electric prostheses (cochlear implants) have opened a world of sound to thousands of deafened adults around the world. Applying the latest technological tools available, NIDCD-supported researchers are continuing to develop diagnostic procedures to predict a person's ability to benefit from an implant, methods of optimizing speech processing strategies, and design and fabrication of new types of cochlear prostheses.

In recent years, deaf children have been implant recipients with some demonstrating remarkable gains in speech understanding and production. Some important issues surrounding the use of cochlear implants in children remain unresolved. These include assessment of optimum habilitation/rehabilitation strategies for development of communication skills; new electrodes that can be removed with minimal trauma to allow later implantation of more sophisticated devices; and insight into development of auditory competency using electric rather than acoustic stimulation.

Usher's Syndrome: Usher's syndrome, characterized by congenital deafness, progressive visual impairment leading to blindness, and, often, mental retardation, may account for as much as 10 percent of all congenital deafness, or 200,000 persons. In a significant advance in this field, NIDCD researchers have recently located the Usher's gene on chromosome 1. Researchers are pursuing this finding and are seeking to fine-map the exact chromosome segment and to characterize and clone the gene, a goal urged in the National Strategic Research Plan. This information can be used to improve diagnosis and genetic counseling and may eventually lead to gene therapy.

Noise: Noise exposure represents the most common preventable cause of hearing loss today. The NIDCD has targeted this area of research for particular emphasis and focus. Institute-supported grantees have determined that the onset and progression of noise-induced hearing impairment is lessened when exposure to that noise is intermittent instead of continuous; that is, periods of quiet allow recovery of hearing to baseline levels. The duration of noise exposure appears to be the critical factor. Therefore, individuals who are at greatest risk for developing hearing loss are those exposed to high intensity noises for long periods of time. This information is important to the understanding of the mechanisms underlying noise-induced hearing impairment and can be used to update the guidelines for occupational noise exposure and counseling young Americans on hearing health care.

The NIDCD and the NIH Office of Medical Applications of Research cosponsored a Consensus Development Conference at the NIH on Noise and Hearing Loss on January 22-24, 1990. The conference brought together biomedical and behavioral scientists, health care providers, and the public, and addressed a broad range of questions, including the characteristics of noise-related hearing loss, acoustic parameters of hazardous noise exposure, individual and age-specific susceptibility, and prevention strategies. The statement drafted by the conference panel provided recommendations and avenues for future research related to noise and hearing loss. The NIDCD is also developing a major public education campaign to address this important area and advise the American public of this preventable form of hearing loss.

Meniere's Disease: Recent studies are providing new insight into mechanisms underlying the development and progression of Meniere's disease. Meniere's disease is a very difficult disease characterized by periods of dizziness, nausea, vomiting, and loss of hearing. While the dizziness is the most prevailing symptom, attacks may also include loud, roaring ringing in the ears; inability to understand speech; altered hearing thresholds; and

gross distortions of sounds. Scientists in one NIDCD research program have demonstrated that an inner ear response to a particular virus, cytomegalovirus (CMV), produces structural and biochemical changes in the cochlea typical of Meniere's disease. CMV, like other herpes viruses, is a lifelong infection which is asymptomatic in most individuals, but which is also known to cause deafness.

Speech/Voice/Language: An estimated 14 million children and adults in the United States suffer from speech and language disorders. Speech disorders may involve any aspect of how words are said, including speech sounds, intonation, pitch, and fluency. The most frequent speech disorders are speech production errors and stuttering. In contrast, language disorders reflect problems understanding what is said, or problems using words and sentences to communicate.

Speech and language disorders have been linked to several factors, including hearing loss in newborns and adults, mental retardation, autism in children, psychiatric disorders in adults, brain damage at birth or resulting from head injury in adolescence or young adulthood, and neurological problems associated with aging, such as Alzheimer's, Parkinson's and Lou Gehrig diseases. Three common speech and language disorders are stuttering, specific language impairment, and aphasia.

Shared Research Facility: A shared national research facility in Madison, Wisconsin, currently offers to scientists the opportunity to simultaneously study lip, tongue, jaw, and soft palate movements without the significant radiation exposure and the tedious analyses usually associated with early attempts to study these movements. The facility is being used intensively by scientists in this country and abroad investigating the entire gamut of speech physiology. In the future, research will focus on peripheral and central mechanisms in the speech of normal subjects and upon the speech impairments associated with stuttering, Parkinson's disease, amyotrophic lateral sclerosis, hearing disorders, and deafness.

Family Studies of Speech Disorders: A longitudinal investigation of familial articulation disorders is nearing completion. The relationship between the articulation skills of parents when they were children and the articulation skills of their children is being evaluated. These studies will provide a better understanding of the genetic and environmental factors that may contribute to the development of functional articulation disorders. Knowledge of the relative contribution of these factors will be invaluable in determining appropriate prevention, treatment, and counseling strategies for families with children who appear to be at risk for functional speech disabilities.

Stuttering: A longitudinal study of young stutterers has recently begun. Their treatment and progress will be monitored for a two-year period beginning shortly after onset of the disorder. Data collected will address the developmental course of childhood stuttering and, in particular, those factors associated with recovery. This study will provide the basis for differential diagnosis and early identification of those children who require intensive therapy for stuttering.

Rehabilitation: Researchers had previously determined that the left side of the brain is associated with language, while the right side of the brain is used for movement and hand coordination, for example, in manual sign language. NIDCD-supported researchers have recently documented a role for the right hemisphere of the brain in communication. Studies are continuing into the effects of right hemisphere brain damage on the interpretation of the meaning of language. This research will contribute to the understanding of the role of the right cerebral hemisphere in language, and will have important implications for designing rehabilitation strategies.

Deafness and Language: A limited number of deaf children attain very high reading levels. NIDCD-supported investigators are striving to determine what abilities enable these deaf persons to excel. Studies are aimed at identifying the abilities that lead to skilled reading and writing by prelingually, profoundly deaf children and adults. By identifying how successful deaf readers achieve their success, this research can be expected to yield results that will significantly influence the reading instruction received by profoundly deaf children.

Balance: Millions of Americans age 17 and older have experienced a dizziness or balance problem. In the United States, there are an estimated 97,000 new cases each year of Meniere's disease, a disorder that affects the inner ear and causes episodes of vertigo, fluctuating hearing loss, and tinnitus (ringing in the ears). In a recent study, balance problems were responsible for more than 6.7 million outpatient visits. The approximate physician costs for these visits totaled $500 million. The inclusion of costs for the associate diagnostic tests brings the full cost to several times this amount.

Balance disorders are quite common. Several groups of people are particularly at risk for different reasons. A majority of people over 70 years of age report problems of dizziness and imbalance, and balance-related falls account for more than one-half of the accidental deaths in the elderly. In a recent study of patients age 65 and older who have been hospitalized for dysequilibrium and imbalance, the average hospital stay was four days. Furthermore, in a sample of persons age 65 to 75, one-third reported that dizziness and imbalance degraded the quality of their lives. Other groups of affected individuals include those with diseases of the vestibular system and healthy individuals exposed to unusual motion environments of land, water, and air and space travel.

Antibiotic Toxicity: Certain antibiotics in common medical use can be toxic to the vestibular system and cause balance problems. The use of these drugs is increasing because of their effectiveness in treating serious bacterial infections arising from a number of causes, including chemotherapy for cancer. While it has been determined that the toxicity of these agents is related to the dosage administered and the duration of treatment, the effect on the vestibular system is usually not detected until the patient's balance function is seriously and irreversibly impaired. NIDCD-supported scientists are working to understand the risk factors and time course of toxicity to the vestibular system from these antibiotics and to refine clinical testing tools for its early detection.

Space: A new area of vestibular (balance) research has been generated by the space program. A number of research needs must be addressed in this area. There is a high incidence of space motion sickness among astronauts during the early stages of travel in the near-zero gravity environment of space. The exact time course and precipitating factors of these debilitating episodes and the countermeasures that may be taken must be understood to enhance the health, safety, and optimal performance of our space mission crews.

Medical Treatment of Balance Disorders: Medical treatment of dysequilibrium often involves the administration of drugs suppressing vestibular system activity. NIDCD-supported researchers are trying to delineate the specific effects of these pharmacologic agents on such debilitating symptoms of balance disorders as vertigo and nausea. This research will lead to a better understanding of the vestibular system and enhance development of more effective pharmacologic agents to treat balance disorders.

Taste and Smell: An estimated 10 million Americans have taste and smell disorders. The predominant problem is a natural decline in smelling ability that typically occurs after age 60. It has been estimated that more than 200,000 persons visit a physician for a smell or taste problem each year. Many more smell and taste disturbances go unreported. Some people are born with chemosensory disorders, but most patients develop them after an injury or illness. Chemosensory disorders may result from polyps in the nasal or sinus cavities, hormonal disturbances, or dental problems. Loss of smell and taste can also be caused by prolonged exposure to certain chemicals, such as insecticides, and by some medicines. Many patients who receive radiation therapy for cancers of the head and neck later complain of disturbances in taste and smell. A person with a faulty sense of taste and smell is deprived of an early warning system that most of us take for granted. Smell and taste sense alert us to fires, poisonous fumes, leaking gas, and spoiled foods. The NIDCD is the focal point within the Federal government for research on taste and smell disorders. The NIDCD supports fundamental studies and clinical investigations of chemosensory disorders at grantee institutions across the nation.

Regeneration: The regenerative capability of the olfactory neuroepithelium and its powerful nourishing action on the brain provides a model system for laboratory studies of repair and rejuvenation of the olfactory system and other parts of the nervous system. The NIDCD is supporting research aimed at learning more about the fundamental and molecular mechanisms of these remarkable regenerative abilities of the olfactory system, which is renewed and remodeled throughout our lives.

That the taste cells regenerate c[illegible]oughout life has long been known. NIDCD-supported investigators are actively seeking to learn more about the mechanisms underlying this regeneration, the maintenance of the taste cells, the interactions between taste cells and nerves and other cells, and the adaptive plasticity of the taste system, which also is renewed and remodeled throughout our lives.

Central Taste Pathways: In comparison to the central pathways of other sensory systems, little is known about the central taste pathways. NIDCD-supported grantees are working to learn more about the basic anatomy and physiology of the central taste pathways and associated neurotransmitters to provide rational approaches for restoring taste function after damage to the system.

Alzheimer's Disease: Anatomical and physiological damage to the olfactory system appears to occur early in the development of Alzheimer's and other savage neurological diseases. The etiology of deficits in olfaction and their predictive usefulness as early warning signs of these neurological diseases is being studied by NIDCD-supported researchers.

Chemosensory Research Centers: With the establishment of chemosensory research centers, opportunities now exist to conduct chemical trials of treatments for nasal-sinus disease and chemosensory disorders. For example, topically applied steroids have shown promise in restoring olfactory function in some patients. The efficiency of pharmacological and surgical treatments must be determined in well-controlled clinical trials.

Touch: Tactile communication aids provide a simple and noninvasive means to rehabilitate the speech and hearing impaired. To take full advantage of this opportunity, NIDCD-supported investigators are striving to develop refined tactile stimulators matched to the complete range of the skin's sensory capabilities.

Centers: In addition to the award of new National Multipurpose Research and Training Centers, the NIDCD is using a somewhat unusual mechanism to widen the opportunity for more institutions to participate in this Centers program in future years. This mechanism is the Exploratory Grants program, which enables institutions with limited experience in setting up multidisciplinary research programs to develop such a program and test it. The awarding of an Exploratory Grant develops and strengthens the research program of the institution and may enable an institution to compete for a Multipurpose Center.

Research Training and Career Development: The NIDCD has targeted research training for particular emphasis. The National Strategic Research Plan provided a blueprint for research studies and served to stimulate increased research efforts in all areas within the mission of the NIDCD. There is a critical need, however, to train scientists to undertake the many research studies that have been identified. New investigators must be trained and established investigators who are currently engaged in research in related areas must be encouraged to bring their skills and expertise to communication sciences and disorders. The panel on training that met in July 1989 provided a number of very specific recommendations for addressing the shortage of researchers in our areas, including postdoctoral candidates, predoctoral students, and experienced investigators. Recommendations that will be pursued by the NIDCD include the immediate recruitment of candidates with Ph.D.s in the basic sciences for research training in communication sciences and creation of a "mentor award program" to increase the cadre of fellows rapidly. The panel urged that efforts should focus on increasing training opportunities for predoctoral students, physicians and basic scientists from

emerging technologies that will increase our understanding of the communication sciences and disorders. Over the next several years and using a variety of targeted mechanisms, the NIDCD will initiate a program to disseminate information about research careers and to recruit students into the communication sciences.

Population-based Studies: Complete epidemiological information is needed regarding the onset, complications, severity, and risk factors associated with congenital and acquired hearing impairment. These factors include age, gender, ethnic origin, cardiovascular status, noise exposure history, familial history of hearing loss, nutritional history, and otologic diseases. Such information will establish a more comprehensive estimate of the incidence and prevalence of hearing loss in the United States, will identify environmental and physiological factors that are related to the presence of hearing impairment, and could lead to the development of a predictive index that would be useful in planning for the needs of hearing-impaired individuals in the future.

Preschool children with Specific Language Impairment (SLI) have inordinate problems in learning, using, and understanding language. These language problems are frequently associated with later academic difficulties, particularly in reading and writing. Previous epidemiologic studies of this population are few, and have tended to include other types of language delays and disorders, such as those related to mental retardation, autism, or hearing loss. Thus, the frequently-cited estimate of 3 to 5 percent of the preschool population is likely to be an inaccurate estimate of children with SLI. In addition, previous studies have been fraught with difficulties in subject criteria and assessment tools utilized, The NIDCD will pursue the acquisition of sound epidemiologic data on the prevalence of SLI in preschool children.

There is an urgent need for a population data base to determine the prevalence of vestibular and balance disorders. The prevalence of various disorders; the signs, symptoms, risk factors, and diagnostic test findings associated with these disorders; and the efficacy of treatment should be recorded and analyzed.

Of all the available epidemiological information, the least is known about the chemical senses. This information must be obtained as part of a population data base and include the prevalence, etiology, demography, risk factors, and efficiency of preventive interventions.

Otitis Media Clinical Trial: Half of all children have ear infections before they reach their first birthday and nine out of 10 children have had ear infections by the time they are 6 years old. Otitis media in children accounts for 10 million physician visits per year and is the leading cause of acquired hearing loss before age 10. Anatomic, physiologic, genetic, and environmental factors contributing to the development of this disease are under investigation. Conjugated vaccines against beta-type Haemophilus influenzae, which is the most common pathogen causing both otitis media and meningitis, are in varying stages of development and require field tests and clinical trials. If proven effective, such vaccines would make a significant contribution to preventing deafness.

Vaccine use in very young children presents a particular challenge. Live vaccines cannot be used in the very young, whose immune systems are immature. Conjugated vaccines must be used in this population. Clinical trials have begun with a commercially available Haemophilus influenzae vaccine to determine its effectiveness against meningitis. The NIDCD will issue a solicitation for research institutions to expand studies of this same family of vaccines and determine its effectiveness in the targeted population of children with early and recurrent otitis media. If the trials demonstrate vaccine efficacy, the most common cause of hearing loss in children under age 9 can be significantly reduced.

Perilymphatic Fistulae (PLF) Clinical Trial: Perilymphatic fistulae (PLF) are tears or defects in one or both of the small, thin membranes between the middle and inner ears. These membranes separate the middle ear space from the fluid-filled inner ear. PLF create abnormal communications between the fluids surrounding the membranous labrynth and middle ear space. The symptoms of perilymph fistula may include dizziness, vertigo, imbalance, nausea, and vomiting. Some people experience ringing or fullness in the ears, and many notice a hearing loss. PLF may occur spontaneously or as a result of head trauma, surgical complications, barotrauma, physical exertion, or congenital anomalies. Although its existence is well documented in the literature, controversy surrounds the differential diagnosis of PLF, intra-operative diagnosis of perilymph in the middle ear, and treatment efficacy. Careful multicenter clinical trials will be undertaken to resolve these issues. The NIDCD issued a Request for Applications soliciting applications for a broad-based multi-institutional trial on this topic.

Intramural Research

1991 Authorization: Indefinite.

Budget Authority:

1990 Appropriation		1991 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA
24	$4,301,000	28	$4,603,000	+4	+$302,000

Purpose and Method of Operation

The mission of the NIDCD Intramural Research Program is to conduct basic and clinical research on the structure, function, and malfunction of the organ of hearing and other sensory organs and the speech producing organs. These efforts range from basic multidisciplinary biological research to clinical trials of newly developed medical and surgical therapies. The Laboratories and Research Clinics are located at the NIH in Bethesda, Maryland.

The most extensively supported science disciplines are audiology, biochemistry, cell biology, genetics, immunology, molecular biology, molecular genetics, neurochemistry, otolaryngology, pharmacology, and speech pathology. The program contributes substantially to the prevention of hearing impairments and other communication disorders by training clinical and basic research scientists. A study of hearing impairments in humans has been initiated. Clinical investigations are aimed at finding new treatments for speech and voice disorders. Brain stem audiology is providing a base line for measuring hearing impairment.

Rationale for the Budget Request

The 1991 budget request for intramural research is $4,603,000, an increase of $302,000 over the 1990 estimate. This level will provide funds for administratiive cost increases, for inflationary costs associated with the purchase of research supplies and services, and a modest increase for four additional FTE's.

Laboratory of Molecular Otology: Genetic factors are known to cause more than 50 percent of all cases of severe childhood deafness. The impact of heredity upon late onset hearing impairments is mostly unknown, but it is thought to be considerable. One in every 1,000 children is congenitally deaf and genetic disorders are responsible for at least half of these conditions. Using recently developed molecular biology and genetic techniques, it is now possible to map the genes whose mutations cause hearing impairments, with a reasonable investment of resources. Mapping of genes is the first step toward finding how they work, what proteins they manufacture, how they produce hearing impairment, and consequently, how early diagnosis, prevention, or treatment might be achieved. Geneticists, otolaryngologists, and audiologists over a large part of the country have been contacted and asked to provide contacts between intramural scientists and families with

genetic hearing impairments. Blood samples from individuals from these families will be collected for extraction of DNA for molecular genetic studies. Initially, the focus will be on the mapping of the gene involved with Waardenburg Syndrome. This hereditary disorder is very likely due to the mutation of one single gene and can give rise to a variety of symptoms of varying severity. Hearing impairment is part of the disorder and can be bilateral or unilateral, severe or very slight. A network has been established by NIDCD scientists for collaboration in efforts to map the Waardenburg gene(s). Families with individuals who have the Waardenburg Syndrome and who are interested in being examined for research on this Syndrome have been located.

In parallel with the studies of the molecular genetics of human hearing impairments, intramural scientists will study genetically caused deafness in mice. It is expected that such studies may provide an understanding of how genes operate in the development of the ear and how, when disturbed at the molecular level, they produce deafness. Genetic studies on mice can be experimentally directed to give information important to studies on humans.

The organ of hearing is extraordinarily sensitive. It can relay a message from a whisper weak enough to fail to move the flame of a candle. Therefore, much interest and research has focused on finding the molecular structure on which this sensitivity is based. The exact nature of the molecules that cause the transduction from mechanical energy of sound waves hitting the auditory sensory cells to electrical-chemical energy inside the sensory cells is unknown. However, it is considered likely that a transducer molecule is an ion channel, of which many types are known. Intramural scientists have initiated a search for the transducer molecule(s), using molecular biology techniques, probing messenger RNA from the organ of hearing, using the very recently developed PCR (Polymerase Chain Reaction) technique and primers for catching and multiplying pieces of DNA that correspond to a great variety of ion channels.

Laboratory of Molecular Genetics: The NIDCD will develop this new Intramural research laboratory. The goal of this laboratory is to study the genetic factors related to deafness, hearing impairment, and speech, voice, olfactory and vestibular disorders. Researchers will seek to map the genes associated with the processes of communication and communication disorders; to study the expression of normal genes in humans and animals, and the corresponding expression of mutant genes that result in disorders of communication processes; to design probes for early diagnosis of genetic abnormalities and disorders; and to offer consultation services for patients undergoing testing or evaluation.

Speech and Voice Unit: The aim of the speech and voice intramural research is to increase our understanding of how speech and voice are produced, the nature and cause of speech and voice disorders, and the development of improved treatments for these disorders. In the next year, both clinical and basic studies are planned. A motion analysis of laryngeal movement in normal speakers and in patients with different disorders will be the first step in developing a computerized biomechanical model of laryngeal function. This model will be developed to improve our understanding of normal laryngeal function and to test new surgical procedures for treating voice disorders prior to their use in patients.

The laboratory is also initiating studies of several new experimental treatments. A double blind crossover study comparing two drugs for the treatment of stuttering will be initiated in children and adults not helped by traditional therapy techniques. In spasmodic dysphonia, a new experimental technique will be used in patients with this rare disorder for which no lasting treatment has as yet been available.

Studies in our intramural laboratories have already been important in demonstrating the neurophysiological control of the larynx in humans. Several laryngeal reflexes are now being studied in normal adults. Experiments are aimed at determining the role of these reflexes as a basis for several voice disorders which are not yet understood.

Clinical Audiology Unit: The intramural Clinical Audiology Unit has 3 major functions: to provide audiology services to all eligible NIH patients, both inpatients and outpatients; to pursue clinical research in primary disorders of hearing and balance; and to continue the development of a unique and innovative approach in applying studies of audiologic phenomena to the broader investigation of many human disorders.

The Clinical Audiology Unit will initiate several new collaborative protocols, including auditory function in autistic adults, auditory function in young adults with dyslexia, defining hearing loss and vestibular function in patients with Retinitis Pigmentosa, and studying hearing loss in Thalassemia and its treatment regimens. In addition, staff will gather audiologic data (including both auditory and vestibular results) on patients with Waardenburg Syndrome to develop a better understanding of the clinical correlates of this hereditary condition. Studies are also planned to search for documented changes in the auditory system function of children with type C Niemann Pick who are undergoing medical treatment for the biochemical defect causing this recessively inherited and fatal neurodegenerative disorder.

In addition, the staff of the Clinical Audiology Unit are developing a new protocol and beginning to study patients with inherited hearing loss. Many patients with a wide variety of hearing losses report that hearing deteriorated some time in infancy, childhood, or early adulthood. Much more clinical data are needed to understand the diversity of clinical manifestations among these populations. When the variety of hearing deficits seen in this condition are understood, researchers can better address correlations with other conditions, causes, and cures.

Research Management and Support

1991 Authorization: Indefinite.

Budget Authority:

1990 Appropriation		1991 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA
38	$4,862,000	42	$5,193,000	+4	+$331,000

Purpose and Method of Operation

This activity includes the extramural program director and staff who are responsible for the scientific planning, direction, administration, and review and approval functions of the Institute's research grant, research contract, and research training programs. The extramural staff is also responsible for the Institute's overall grants and contracts administration including processing, award, and management activities. This activity also supports the immediate Office of the Director and the staff which assist the Director in management and direction of the Institute's programs. These units include the administration and financial management activities of the Institute as well as program analysis functions and scientific and health reporting.

Rationale for the Budget Request

The 1991 budget request for research management and support is $5,193,000, an increase of $331,000. This level will provide funds for built-in increases, inflationary costs associated with the purchase of supplies, and a modest increase to support four FTEs.

As the need for sound epidemiologic data exists in all areas within the NIDCD mission, the Institute is planning to establish an Epidemiology Section. This Section could utilize the extensive data base that already exists to obtain a current estimate of the incidence, prevalence, and risk factors for both genetic and acquired deafness and hearing impairment. In this study the data accumulated through the National Health and Nutrition Examination Surveys (NHANES) I, II, and III would be analyzed to correlate audiometry and self-reported hearing loss and to assess the relationship between hearing level and age, nutritional history, cardiovascular status, gender, and ethnic origin. These analyses will serve two important purposes: to establish a more comprehensive estimate of the incidence and prevalence of hearing loss in the United States and to identify environmental and physiological factors that are statistically related to the presence of hearing impairment. This Epidemiology Section will also initiate studies of disorders of speech, voice, language, vestibular function, and the chemical senses.

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Detail of Permanent Positions

	1989 Actual	1990 Appropriation	1991 Estimate
ES-5	-	1	1
ES-4	4	4	4
ES-3	-	-	-
ES-2	-	1	1
Subtotal	4	6	6
GS/GM-15	1	4	5
GS/GM-14	4	5	6
GS/GM-13	3	5	6
GS-12	-	6	7
GS-11	4	5	6
GS-9	3	3	4
GS-8	1	4	4
GS-7	3	4	5
GS-6	2	6	6
GS-5	2	3	4
GS-4	-	4	4
Subtotal	23	49	57
Upgraded	7	7	7
Total permanent positions	34	62	70

National Institute on Deafness and Other Communication Disorders

New Positions Requested

		1991	
NIDCD Intramural Research	Grade	Number	Annual Salary
Otolaryngologist	GS-15	1	$59,216
Molecular Biologist	GS-14	1	50,342
Technician	GS-11	1	29,891
Technician	GS- 9	1	24,705
		4	$164,154
NIDCD Research Management and Support			
Deputy Director, NIDCD	SES	1	84,000
Health Scientist Administrator	GS-14	1	50,342
Epidemiologist	GS-14	1	50,342
Statistician (Health)	GS- 9	1	24,705
		4	$209,389

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Advisory and Assistance Services

For FY 1991, the Advisory and Assistance Services budget will be $63,000, an increase of $2,000 over the 1990. These funds will continue to support a variety of services that permit the Institute to meet the mandates of its authorizing legislation.

The Institute was established October 28, 1988. Included within that legislation was a formally established National Deafness and Other Communication Disorders Advisory Board. The Advisory Board is charged with the role of advising and making recommendations to the Director, NIDCD on the implementation of the National Strategic Research Plan. A National Institute on Deafness and Other Communication Disorders Advisory Council also ensures that the Institute meet its statutory and regulatory requirements for peer review.

Policy guidelines exist in the form of OMB Circular A-120 and DHHS General Administration Manual 8-15. Each year a consultant sercices plan is prepared identifying planned AAS procurement. The NIH accounting system contains Common Account Numbers (CANS) that have been designated for use in identifying and aggregating costs for AAS.

MONDAY, MARCH 19, 1990.

NATIONAL CENTER FOR RESEARCH RESOURCES

WITNESSES

DR. ROBERT A. WHITNEY, JR., ACTING DIRECTOR
DR. WILLIAM F. RAUB, ACTING DIRECTOR, NIH
DR. JUDITH L. VAITUKAITIS, ACTING DEPUTY DIRECTOR, NCRR
RICHARD L. SHAFER, EXECUTIVE OFFICER, NCRR
ANNE E. SUMMERS, BUDGET OFFICER, NCRR
DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DHHS

Mr. NATCHER. We take up now the National Center for Research Resources. We have before the committee Dr. Robert A. Whitney, Jr., the Acting Director. Dr. Whitney, before you give us your statement tell us who you have with you at the table.

Dr. WHITNEY. Thank you.

Dr. Vaitukaitis, the Deputy Director on my right, Mr. Shafer, Executive Officer, NCRR, and Mrs. Summers, the Budget Officer for NCRR.

Mr. NATCHER. We will be pleased to hear from you.

Dr. WHITNEY. Thank you, sir.

OPENING STATEMENT

Mr. Chairman and members of the committee, I am pleased to present the President's request for the fiscal year 1991 Research Resources appropriation. Since 1962 this appropriation has provided much of the infrastructure support that facilitates the conduct of extramural research funded by the categorical Institutes of the National Institutes of Health, and other research programs supported by the Public Health Service.

I am pleased to be able to tell you that the Secretary has recently approved the establishment of the National Center for Research Resources, merging the Division of Research Resources' extramural programs with the former Division of Research Services' intramural programs.

Today I will be speaking of the extramural programs since the Research Resources budget request is entirely extramural. The Center's six extramural programs provide critical resources, from state-of-the-art equipment to dedicated clinical research beds and human cells, essential to the conduct of the nation's biomedical research. I will briefly describe each program.

The clinical research program supports a network of 78 geographically dispersed centers, located within either teaching hospitals or research institutions, where scientists can study normal physiology and disease processes in both adults and children. The centers provide highly skilled research nurses, as well as special-

ized laboratories and support facilities for inpatient and outpatient research, to facilitate the conduct of high quality clinical research, providing the infrastructure essential for carrying out clinical trials and other types of clinical research funded by other NIH and other PHS components. The centers also support the Clinical Associate Physician (CAP) program which provides the opportunity for junior physicians and dentists to enter clinical research careers.

In 1989, more than 7,250 investigators utilized these centers for their research projects. These researchers received more than $550,000,000 in primary research funding from the categorical institutes of the NIH as well as another $150,000,000 from other sources. This national network of General Clinical Research Centers will continue to be the essential interface between basic and clinical research.

The GCRCs continue to host a wide variety of research projects, both AIDS-related and other in children and adults, which are producing exciting results. A recent study revealed that the drug deprenyl delays the onset of disability in patients with early, otherwise untreated Parkinson's disease.

Another group of investigators has developed a method for the rapid, early and definitive detection of HIV infection in infants at high risk for acquired immunodeficiency syndrome or AIDS. This will allow for early treatment of infected infants and clear others who are suspected of infection. At another center a method is being developed that may be effective in rapidly identifying early cases of Alzheimer's disease.

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Technology is the engine that drives today's biomedical research. Our Biomedical Research Technology Program provides the scientific community access to advanced technologies needed as tools to solve the problems of biomedical research. The program funds centers for the development and application of essential technologies that are not widely available. The centers are staffed by gifted scientists and engineers who work closely with biomedical scientists from academia, industry and other laboratories both to develop and to apply new technological capabilites to cutting-edge biomedical research problems. The new technologies developed by this program have significant applications and I will give a couple of examples.

In the molecular area, a new beam line that can be used for X-ray diffraction studies of crystalline viruses and proteins from pathogenic sources was funded in 1989 at the Cornell High Energy Synchrotron Source. This will be the only synchrotron facility in the world with a biological containment capability to permit the structural studies of crystalline infectious agents such as poliovirus and coat proteins from the AIDS virus and its receptors.

A different type of structural research collaboration between a scientist at the University of California, Berkeley, and the mass spectrometry center in San Francisco resulted in the determination

of the chemical nature of the signalling mechanism used by bacteria to control the proteins involved in their motion.

The chemical basis for cellular motility is a major unsolved problem in cell biology; if this signalling mechanism, which can only be studied using novel analytic methods and a very advanced mass spectrometer, proves to be widespread, it will have far-reaching implications for molecular interpretation of cellular behavior.

Our Laboratory Animal Sciences and Primate Research (LASPR) Program develops and supports animal resources and facilities for biomedical research, including the identification and development of new and more appropriate animal models of human disease. The seven Regional Primate Research Centers provide specialized facilities and environments to support a broad range of biomedical research projects related to human health disorders using nonhuman primates. They serve more than 1,300 biomedical researchers in the United States.

The Laboratory Animal Sciences Program supports activities related to the diagnosis and control of laboratory animal diseases, special animal colonies, animal model development, post-doctoral training programs in laboratory animal medicine, and the improvement of laboratory animal facilities at biomedical research institutions.

In 1990, NCRR announced two programs for laboratory animal facilities, one targeted to small institutions receiving less than $500,000 in PHS funds and the other for larger schools. The AIDS Animal Models Program supports breeding and breeding-associated research on chimpanzees and retrovirus/herpes-virus free colonies of rhesus monkeys for use in PHS-supported research on vaccine development and therapeutic approaches for human AIDS.

The LASPR program has helped to produce one of the most exciting developments yet seen in the area of AIDS vaccine development. A team of investigators at the Delta Primate Center in Louisiana recently developed a prototype vaccine, made from a virus that infects rhesus monkeys, that has prevented the animals from becoming infected with simian AIDS, a disease that shares many characteristics with human AIDS. This achievement is encouraging evidence that it may be possible to develop a vaccine to protect humans from the virus that causes AIDS.

The Center's Biomedical Research Support Program, consisting of three subactivities, is designed to strengthen institutional research in the health sciences. The oldest of these subactivities, the Biomedical Research Support Grant (BRSG) formula program has provided flexible funds on a formula basis to institutions to support biomedical research needs not served by other support programs and for purposes that could best be identified at the local level by the grantee institutions. Principal uses of BRSG funds have been support for pilot studies, interim funding for active research programs, young investigator support, and provision of central resources.

The budget request for 1991 includes $17,700,000 for a significantly altered BRSG formula program. In response to changing demographics and a growing need to attract more individuals to biomedical research, one third of the program in 1991 will be focused on an effort to encourage underrepresented minorities and the eco-

nomically disadvantaged to become active in the nation's research enterprise. The remaining $11,800,000 will be used for the traditional BRSG formula program.

A second subactivity of the BRS program is Shared Instrumentation Grants (SIG), which are awarded to multiple investigators, each with PHS grant support, as shared resources. Progress in medical research depends heavily upon instruments; many advances in basic and clinical research have been possible only because advances in instrumentation have opened up new, more sensitive and accurate ways to conduct scientific research. The SIG program helps institutions buy new instruments and upgrade older equipment. The program supports instruments that cost $100,000 or more, and the equipment must be shared by three or more PHS-supported investigators at an institution. The 1991 budget request continues support for this program at the 1990 level.

The Minority High School Student Research Apprentice Program (MHSSRAP), the third BRS subactivity, provides health-related research experience to minority high school students at institutions with BRSG or Minority Biomedical Research Support funding. The program is designed with the expectation that exposure to such experience will result in many of these students choosing careers in biomedical sciences. Since its beginning in 1980, the program has provided hands-on work in basic and clinical laboratories to over 8,000 apprentices, many of whom have gone on to careers in health-related fields.

The 1991 budget request for the Center includes an increase of $836,000 for this program which will provide the support for 1,764 apprentices and begin a program for high school science teachers.

The Biological Models and Materials Research Program was recently established in the Center to underscore the importance of providing for the development and support of nonmammalian models such as cell systems, lower organisms and nonbiological systems for biomedical research, and to provide critically important biological materials to the research community. This program received a large increase in 1990 which has allowed expansion, including the initiation of the first research project grant program for the center in many years. The 1991 request continues this program at approximately the 1990 level.

In December of 1989, the Center issued a request for applications for research projects on various alternatives to the use of animals in research. This represents the first time that NIH has issued such a request and demonstrates a commitment to finding and developing alternatives to using animals in research, options that can be used when appropriate instead of animals. The response to this request for applications has been encouraging and several excellent projects are expected to be funded in 1990.

This year for the first time the budget request for the Center includes funding for the Research Centers in Minority Institutions (RCMI) program. Although funds have previously been appropriated to the Office of the Director, the Center has always administered the program. Initiated in 1985, the RCMI program provides the resources to expand the capacity of predominantly minority, doctoral degree granting institutions to perform biomedical research, by increasing staff expertise and technical knowledge and

by upgrading scientific instrumentation. The program currently provides support to 17 institutions.

The expansion of the research capacity of RCMI grantee institutions will enable them to become full participants in biomedical research related to the infectivity of the AIDS virus and to the human genome initiative, especially as this research impacts on minority populations. The need for RCMI institutions to address the health research needs of this country has never been more urgent than now with the AIDS epidemic's disproportionate impact on minority populations. RCMI grantee institutions are located in the midst of the affected populations, and their historic role has been to address the health problems and issues that affect these populations.

With respect to the human genome question, as with AIDS, there are significant and important research questions that must be addressed for minority populations. Here, again, RCMI institutions are ideally located to work with minority populations. A core immunogenetics laboratory, supported by an RCMI program award, is becoming capable of genetic studies as they relate to human leukocyte antigen (HLA) phenotypes in patients with HLA-associated diseases. This RCMI program thrust will be expanded in order to participate in other human genome research.

The 1991 budget request for the Center includes an increase of $5,300,000 or 30 percent for the RCMI program. The increase will allow for increased emphasis on research on ethnic-specific diseases and expanded involvement in AIDS clinical trials, and the possible funding of newly eligible institutions.

The 1991 Research Resources budget request for AIDS includes an increase of approximately 5 percent, which will be shared by all the programs.

The total 1991 Research Resources budget request is $319,151,000. I will be happy to answer any questions you may have.

[The information follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Center for Research Resources

Mr. Chairman and Members of the Committee: I am pleased to present the President's request for the Fiscal Year 1991 Research Resources appropriation. Since 1962, this appropriation has provided much of the infrastructure support that facilitates the conduct of extramural research funded by the categorical Institutes of the National Institutes of Health, and other research programs supported by the Public Health Service. I am pleased to be able to tell you that the Secretary has recently approved the establishment of the National Center for Research Resources, merging the Division of Research Resources extramural programs with the Division of Research Services intramural programs.

Today I will be speaking of the extramural programs since the Research Resources budget request is entirely extramural. The Center's six extramural programs provide critical resources - from state-of-the-art equipment to dedicated clinical research beds and human cells - essential to the conduct of the nation's biomedical research. I will briefly describe each program.

The Clinical Research Program supports a network of 78 geographically dispersed centers, located within either teaching hospitals or research institutions, where scientists can study normal physiology and disease processes in both adults and children. The centers provide highly skilled research nurses, as well as specialized laboratories and support facilities for inpatient and outpatient research, to facilitate the conduct of high quality clinical research, providing the infrastructure essential for carrying out clinical trials and other types of clinical research funded by other NIH and PHS components. The centers also support the Clinical Associate Physician (CAP) program, which provides the opportunity for junior physicians and dentists to enter clinical research careers.

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The budget request for 1991 includes $17.7 million for a significantly altered BRSG formula program. In response to changing demographics and a growing need to attract more individuals to biomedical research, one third of the program in 1991 will be focused on an effort to encourage underrepresented minorities and the economically disadvantaged to become active in the nation's research enterprise. The remaining $11.8 million will be used for the traditional BRSG formula program.

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provided hands-on work in basic and clinical laboratories to over 8,000 apprentices, many of whom have gone on to careers in health-related fields.

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human leukocyte antigens (HLA) phenotypes in patients with HLA-associated diseases. This RCMI program thrust will be expanded in order to participate in other human genome research.

The 1991 budget request for the Center includes an increase of $5.3 million or 30 percent for the RCMI program. The increase will allow for increased emphasis on research on ethnic-specific diseases and expanded involvement in AIDS clinical trials, and the possible funding of newly eligible institutions.

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The total 1991 Research Resources budget request is $319,151,000. I will be happy to answer any questions you may have.

Biographical Sketch

ROBERT A. WHITNEY, JR., D.V.M.

Robert A. Whitney, Jr., D.V.M., is Director of the National Center for Research Resources (NCRR), National Institutes of Health, Bethesda, Maryland. He is also Director of the NIH Office of Animal Care and Use, and Chairman of the U.S. Government Interagency Research Animal Committee.

A native of Oklahoma, he received his D.V.M. degree from Oklahoma State University in 1959 and the M.S. in pharmacology from Ohio State University in 1965; he was board certified in laboratory animal medicine in 1966.

In the U.S. Army, Dr. Whitney served as director of the Army Veterinary Corps' postdoctoral training in laboratory animal medicine and as a consultant to the Army Surgeon General for laboratory animal medicine. He transferred to the National Institutes of Health in 1971 as a US Public Health Service Commissioned Officer. Initially a special projects officer in the Division of Research Resources, he was Chief of the Veterinary Resources Branch, Division of Research Services, from 1972 to 1985, when he became Division Director. He is an Assistant Surgeon General in the U.S. Public Health Service Commissioned Corps and served as Chief Veterinary Officer from 1984 to 1989.

Dr. Whitney's primary interests are comparative medicine and primatology. In 1977 he was president of the American Association for Laboratory Animal Science. He is also a past president of the Washington, D.C., Veterinary Medical Association. He has been a member of the Executive Committee and the Advisory Council of the Institute for Laboratory Animal Resources, National Research Council. He also serves as a consultant to the Pan American Health Organization and the World Health Organization, and Chairman of the NIH Animal Care and Use Committee.

Dr. Whitney is co-author of one book and author or co-author of 39 scientific publications on aspects of laboratory animal science and comparative medicine. He is an associate editor of the Journal of Primatology and the Journal of Medical Primatology.

His awards include the US Public Health Service Distinguished Service Medal; the USPHS Surgeon General's Exemplary Service Medal, Meritorious Service Medal and Commendation Medal; the NIH Director's Award; the AVMA Charles River Prize, Karl F. Meyer Award and the Department of the Army Legion of Merit, Meritorious Service Medal, and Commendation Medal.

NEW NATIONAL CENTER FOR RESEARCH RESOURCES

Mr. NATCHER. Thank you, Dr. Whitney. Doctor, your organization has undergone a merger since last year's hearings. Would you describe to the committee the new National Center for Research Resources and its components?

Dr. WHITNEY. The Division of Research Resources which has had the extramural program of the Center is now joined by an intramural program comprised of four elements: a Biomedical Engineering and Instrumentation Program, which is analogous in many ways to the Biomedical Research Technology Program of the old DRR; the Veterinary Resources Program which is analogous in many ways to the Laboratory Animal Sciences and Primate Research Program; and we have two other branches, the NIH Library and Medical Arts and Photography, that provide direct support to investigators at NIH.

The traditional programs of the Division of Research Resources I spoke to a few moments ago remain in the same traditional composition that we have had up until the merger. So we now have an intramural component to accompany and augment our extramural activities.

MINORITY BIOMEDICAL RESEARCH SUPPORT

Mr. NATCHER. Review for the committee the reason the Minority Biomedical Research Support program was transferred from your organization to General Medical Sciences.

Dr. WHITNEY. There was an in-depth review last year of the programs of the Division of Research Resources and also of the principal minority programs funded by the National Institutes of Health.

At that time it was decided that because the Minority Biomedical Research Support Program was primarily a program designed to prepare minorities for careers in reserach, it would fit best in NIGMS which has a large role in the training of new investigators for NIH. The Research Centers in Minority Institutions Program was moved from the Office of the Director into the Division of Research Resources because of its role of providing infrastructure support which has been DRR's mission over the years.

GENERAL CLINICAL RESEARCH CENTERS

Mr. NATCHER. Why are you proposing less than a 1 percent increase in funding for the clinical centers, especially when they are facing major cost increases for nursing?

Dr. WHITNEY. As is the case with NIH activities other than genome, AIDS and minority programs, the General Clinical Research Centers have a flat budget.

Mr. NATCHER. How much revenue do the clinical centers receive from third party insurers and how has this changed over time?

Dr. WHITNEY. I cannot give you the exact amount of dollars from the third party insurers. It is in the neighborhood of $10,000,000. This has been decreasing over the last few years as third party payers are refusing more and more to pick up usual and customary hospitalization costs if the patient participates in research projects.

I would be happy to provide more details of that for the record.

Mr. NATCHER. All right.

[The information follows:]

THIRD PARTY REIMBURSEMENT

There has been a progressive decline in the number of research patient days reimbursed to centers over the past few years by third party carriers. Several factors are at work. Preadmission clearance by insurers has been a factor along with some third party carriers retroactively denying reimbursement for those patients who have signed consent forms to participate in a research protocol even if established medical care or therapy is provided during the admission for which the patient was in the hospital. Informed consent is a requisite for conducting any clinical research protocol, even if the research constitutes only a small fraction of a single inpatient day.

In 1984, there were 53,288 patient day credits from third party carriers which generated $10.4 million to offset the cost of operating the general clinical research centers. In 1988, there were 32,943 patient day credits from third party carriers which generated $9.8 million to offset the cost of operating the general clinical research centers. The average credit offset per research day was $194 in 1984 and $299 in 1988.

Mr. NATCHER. How does patient cost at the general clinical research centers compare to those at the NIH clinical center, Doctor?

Dr. WHITNEY. I am not aware of any comparison of those costs having been made, Mr. Chairman.

Mr. NATCHER. Since resources for the clinical centers are so limited, have you considered reducing the number of awards that you make, Doctor?

Dr. WHITNEY. Yes. In 1990 the comparable number of centers will decrease from 78 to 75. Three centers will split to become separate adult and pediatric centers, so the actual count will remain 78.

BIOMEDICAL RESEARCH SUPPORT GRANTS

Mr. NATCHER. As you know, Doctor, the committee has previously disagreed with your proposal to reduce biomedical research support grant funding. Has any new information emerged during the past year to provide a better programmatic basis for this cut?

Dr. WHITNEY. The information that I am aware of that has been developed over the last year interestingly has indicated that about one-third of the BRSG money is used in pilot projects, about one-third is used in supporting investigators between grants and about one-third has been used for resource improvements within the institutions. All of this is in direct support of the research project grant holders.

However, the priority placed on RPGs remains higher than that of the BRSG.

MINORITY HIGH SCHOOL PROGRAM

Mr. NATCHER. Tell us about your proposal to set aside one-third of the biomedical research support grants for institutions serving minorities and the disadvantaged.

Dr. WHITNEY. Yes, sir. Of the $17,700,000 requested in the President's budget for the BRSG program this year, we intend to set aside nearly $6,000,000 for programs that will allow us to bring more minority high school students into the research experience next summer.

These funds, together with the money from the traditional support for the minority high school apprentice program, will allow us to provide, as I mentioned in my opening statement, an experience for over 5000 minority students next year.

We also hope to involve 200 or more high school science teachers from that same community in a pilot training program. You have heard many times during these hearings about the problem of bringing young people into research and the effort we need to make in that area, especially in recruiting minorities. This has a very high priority within the NIH system.

Mr. NATCHER. Will this funding be allocated by a separate formula?

Dr. WHITNEY. No, this will not be allocated by the separate formula. The eligibility requirements would be the same as they have been in the past. Those institutions receiving BRSG support or Minority Biomedical Research Support grants will also be eligible for the Minority High School Student Research Apprentice Program dollars.

Mr. NATCHER. Would you have to have new legislative authority?

Dr. WHITNEY. No, sir.

Mr. NATCHER. Would the one-third funding be restricted to minority institutions?

Dr. WHITNEY. It would be restricted to minority students but not minority institutions.

BIOMEDICAL RESEARCH SUPPORT GRANTS

Mr. NATCHER. The number of biomedical research support grants increases in 1991. You are proposing to reduce funding by $27,000,000. How do you do that, doctor?

Dr. WHITNEY. There will be no change in the eligibility requirements for the institutions to compete for BRSG money. We are intending to make awards in the range of $5,000 to $30,000, considerably lower than what is available in the 1990 budget.

BIOLOGICAL MODELS AND MATERIAL RESEARCH

Mr. NATCHER. Will the development of biological materials and modeling eventually reduce the use of mammals in research, especially primates?

Dr. WHITNEY. That is possible, but I don't believe likely in the near future. There are many reasons to use alternatives to higher animals in research, and indeed some research requirements can best be met in more simple systems.

However, for the most part, before bringing any drug or new therapy or vaccine for clinical trials in human beings, it is necessary to use higher animals. Perhaps we will be able to use fewer but I cannot say we will be able to reduce significantly the number of higher animals we will be using in the near future.

Mr. NATCHER. Last year this committee doubled funding for biological materials and modeling. How are these funds, as later modified in conference, being used?

Dr. WHITNEY. In 1990 we started a new program to be funded by the standard research project grant. This is a program that would stimulate development and use of non-traditional models that might be used as substitutes for higher vertebrate models. We have published a request for applications and have had a very good response from people looking at non-mammalian models, proposing doing research as well as providing resource support.

Mr. NATCHER. Doctor, do most of your biological materials funds go to support the supply of materials rather than research into new uses of non-mammal models?

Dr. WHITNEY. Yes, at this point I would say that is true. Most of our BMMR funds are designated as resource funds rather than actually developing new non-mammalian models. The new research project grant program is slated to help increase development.

RESEARCH PROJECT GRANTS

Mr. NATCHER. Why haven't you requested funding for any new research grants in this area in 1991, Doctor?

Dr. WHITNEY. Within the constraints of the budget within the NCRR we wanted to take a look at what kind of response we had this year. Hopefully we will ask for more funds in the future for this program if it proves to be as effective as we expect.

Mr. NATCHER. Thank you.

Mr. Conte, I yield to you.

Mr. CONTE. Thank you, Mr. Chairman.

Dr. Whitney, I join the chairman in welcoming you back this year. You have got your work cut out for you, now that the two divisions for research support have been merged into a new center. The committee appreciates the cooperation you have shared with us. Keep up the good work.

ANIMAL FACILITY IMPROVEMENTS

Your program had the foresight to set-aside a portion of your animal facility improvement grants for small institutions. Many small institutions are doing excellent work in biomedical research. Smith College is building a solid program in the sciences, and the improvement of their animal facilities is crucial to their program. What is the status of this competition? Is there a future need for grants targeted for small institutions such as Smith College? Will you keep me informed on the grant application process?

Dr. WHITNEY. Yes, sir, I will. We have had a very good response to this competition. The first group of applications is currently under review. I think the primary benefit of this new program is that it separates the smaller institutions from the larger for competitive purposes. The program also does not require them to have matching funds for their projects.

We are very pleased that we have had a good response. We hope to continue the program and hope it will grow.

INTRAMURAL ANIMAL FACILITIES

Mr. CONTE. NIH requested $18,500,000 for upgrading your intramural animal facility. Although this is part of the Buildings and Facility request, perhaps you can tell the committee something about the longer range needs and plans for the intramural infrastructure at NIH from your Center's perspective. What role will Building 49 play in meeting those needs and is there a similar need for the extramural community?

Dr. WHITNEY. Yes, sir. The $18,500,000 requested in the President's budget for the intramural animal facilities should allow NIH to apply for accreditation by the American Association for the Ac-

creditation of Laboratory Animal Care in December of this year. Over the long range we will be asking for additional money to upgrade other animal facilities that are 35 to 40 years old in order to maintain accreditation.

Building 49 is absolutely essential in this process of accreditation. Without Building 49 the NIH program in neurobiology, particularly as it uses primates in the research on the campus, would not be able to continue.

In the extramural programs we see similar needs. As I alluded to earlier, the animal facility improvements program has been meeting those needs over a number of years, with approximately 40 grants a year for research animal facility improvements.

This program has helped a number of institutions become accredited. We see no end in sight of the need for upgrading animal facilities. As new facilities come in, other facilities grow older and need upgrading and renovation.

BIOLOGICAL MODELS AND MATERIALS RESEARCH

Mr. CONTE. Last year the committee expressed strong support for "The Biological Models and Materials Research Activity" which continues to support the exploration and development of alternatives to the use of mammalian animals in biomedical research and urged that additional funding be provided for this activity.

How much additional funding was provided for biological models and materials research in 1990? What are these funds being used for and will this program's success reduce the number of animals used in biomedical research and toxicological testing?

Dr. WHITNEY. In 1990 the budget for this program was increased by approximately $1,600,000, almost a 50 percent increase. As I mentioned earlier this increase has allowed us to begin a program supported by research project grants on developing non-mammalian and non-animal models. We believe that, yes, there will be some future impact from this program.

But as I mentioned earlier, I believe that in the near future there will be a continuing need for higher animals. I think there are certain questions that can best be answered in lower systems and should be.

Certain questions can also be answered with mathematical modeling, computer simulation, and physical modeling. However, in the final analysis, all those questions have to go to higher animals before they can be taken to human beings.

RESEARCH FACILITIES IMPROVEMENT

Mr. CONTE. In 1988 and 1989 your Center received funds to support the Research Facilities Improvement Program. No funds were requested in 1990 and no funds have been requested in 1991. Does this mean that this program is no longer needed?

Dr. WHITNEY. No, sir. Of the 115 applications that we received in 1989, 50 awards were made. We believe that were funds available for additional solicitations, many more meritorious applications would be received.

We are aware of many institutions out there, both those doing AIDS research and others who are not, who require the kind of in-

vestment that the Research Facility Improvement program allowed.

EXTRAMURAL CONSTRUCTION

Mr. CONTE. We know your colleagues at NIH have considered various authorizations of construction for NIH and specifically for your Center. Would you comment on what you consider in your professional judgment to be the need for such authority at this time?

Dr. WHITNEY. Yes, sir. This was a problem both with the Research Facility Improvement program and the Primate Research Centers program. With the AIDS research in particular a considerable amount of renovation was required to provide proper facilities for the research. Those renovations for the most part were done though there is still a need for more. On the other hand, the Primate Research Centers and many other institutions across the country require more than just renovations to upgrade facilities to meet the current sophisticated requirements. Construction authority would be very helpful.

BIOMEDICAL RESEARCH SUPPORT GRANTS

Mr. CONTE. The National Advisory Council on Research Resources has continually urged NIH to restore and increase the funding for the BRSG program. This budget does not do that. What do you see as the alternative source of funding for pilot research if BRSG is so dramatically reduced? Is it true that these funds are used according to local decisions about research support?

Dr. WHITNEY. Yes, sir, it is true. I see no alternatives to the BRSG for the funding of pilot studies and other local uses of the funds that the BRSG program supports..

Mr. CONTE. Is every use of BRSG grant money reviewed by a local advisory committee similar to the NIH study sections?

Dr. WHITNEY. Yes, sir, it is. As I mentioned earlier one-third of the funds go toward the funding of pilot studies which are very important and frequently lead to the submission of applications for traditional research project grants. About one-third go into the support of researchers who are between grants, and about one-third go into infrastructure such as animal resources and equipment and emergency needs.

Mr. CONTE. Do you think the NIH request for RPG increase of $227,000,000 will offset the BRSG loss?

Dr. WHITNEY. No, sir, I don't.

Mr. CONTE. Have BRSG supported pilot projects led to a successful RPG application in the past?

Dr. WHITNEY. Yes, sir. We estimate about 18 to 20 percent of the successful RPG's go to researchers formerly supported by BRSG funds.

Mr. CONTE. How will institutions accumulate preliminary data for future RPG applications if BRSG is cut?

Dr. WHITNEY. I don't know, I can't answer that.

INTRAMURAL/EXTRAMURAL COOPERATION

Mr. CONTE. What are some examples of the development of resources supported by your center and how does this R&D benefit the extramural community and how does it help the intramural scientists?

Dr. WHITNEY. One of the resources supported within our intramural program is an animal genetic resource where we develop animal models such as immuno-deficient mice. These are sent to investigators in this country and around the world. The intramural program in that respect contributes greatly to extramural research activity.

These animals are now being used in AIDS research, bone marrow transplant research and some of the gene therapy work that is so exciting and of such high priority at NIH.

This cooperation also works in reverse. Our entramural chimpanzee breeding program supplies animals to intramural researchers working on AIDS vaccines as well as to extramural researchers.

RESEARCH CENTERS

Mr. CONTE. I understand the National Advisory Council on Research Resources has recommended funding for your research centers that are about 20 percent higher than you are currently asking. Is that true? What do you estimate is the effect on the researchers of this constrained funding?

Dr. WHITNEY. That is true of the Biomedical Research Technology Centers and the General Clinical Research Centers. It is somewhat lower for the other programs. The reduced funding has had a profound impact on our ability to support those two programs.

Mr. CONTE. NIH is requesting an increase of 5.4 percent over 1990 in research project grants. Now these grants provide the lion's share of the use for the research resources your center develops and supports. Yet NCRR's request for most programs is level-funded, and for BRSG it is drastically lower.

Is it correct to conclude that these grantees will not need the research resource support that has been needed in the past?

Dr. WHITNEY. No, I don't think that is a correct conclusion. However, without the research project grants the system would not be needed anyhow. So priority has to be with the research project grants.

CURRENT SERVICES REQUIREMENTS

Mr. CONTE. How much more money would your Center need to maintain current services?

Dr. WHITNEY. Current services could be maintained with approximately $39,000,000 of additional funds.

NEW TECHNOLOGIES

Mr. CONTE. We are beginning to hear in the news more and more about the possibilities brought to research by new technologies such as synchrotron radiation and M.R.I. imaging. Tell us what

your Center is doing to advance the use of these technologies by biomedical researchers.

Dr. WHITNEY. The BRTP program supports a number of these activities, and at the moment has a window of opportunity to participate in others. A large synchrotron facility developed by the Department of Energy allows us the opportunity to use this resource. The nuclear magnetic resonance imaging is very sophisticated and is also used by the medical community with BRTP funding.

Traditionally, the National Center for Research Resources has been the place for the continued development of sophisticated resources and training investigators to use all this highly sophisticated equipment across the research community supported by NIH.

Mr. CONTE. Can you support these activities with your current fiscal year 1991 budget request?

Dr. WHITNEY. We can support a portion of them. We cannot support the 59 centers that were indicated for 1990 at the time the budget was prepared. We will probably support somewhere around 55 centers.

Mr. CONTE. In your professional judgment what is needed to take advantage of the most pressing needs of researchers and of the advances being made in physical and engineering sciences?

Dr. WHITNEY. In my professional opinion it would take an additional $15,000,000 a year. I think the time is uniquely opportune right now for that investment because of several Department of Energy activities that are being developed that we could develop biomedical application for. If we could increase the BRTP program by $15,000,000 a year to support these activities, along with an additional $5,000,000 to develop similar activities, such as those at Berkeley, the Argonne Laboratory and the National Institute of Science and Technology with their free electron laser, we could contribute a great deal to biomedical research.

Mr. CONTE. How is this program related to the Shared Instrument Grant program?

Dr. WHITNEY. The shared Instrumentation Grant program is the end result of the BRTP program. When these highly sophisticated instruments required for biomedical research have been developed by the BRTP and brought to a point where they are of practical value and available commercially, then the Shared Instrument Grant program takes over to provide researchers the funds for those high ticket items that cost over $100,000.

Our support for these instruments ranges from $100,000 to $400,000. Some of these instruments may cost up to $1,000,000 but we can only provide a maximum of $400,000. This program is the next step after the development program, after the instruments have become the commercial available.

Mr. CONTE. I yield to my good friend from Ohio, Mr. Stokes.

Mr. STOKES. Thank you, Mr. Conte.

I welcome you back to our committee again, Dr. Whitney.

MINORITY HIGH SCHOOL PROGRAM

On page 5 of your program where you talk about the altered BRSG formula you say, "In response to changing demographics and a growing need to attract more individuals to biomedical research,

one-third of the program in 1991 will be focused on efforts to encourage underrepresented minorities and the economically disadvantaged to become active in the nation's enterprise."

Tell us about the need for that. What do you mean by that statement?

Dr. WHITNEY. I think we all recognize that there is an acute need to bring minority students into the sciences. There are a number of programs at the pre-baccalaureate, baccalaureate and post-baccalaureate levels that you are familiar with, MBRS, MARC and others. But there are no programs other than the high school minority apprenticeship program that are aimed at students below the college level at this time.

I think most people agree with me that if we don't start at the high school level introducing students to the sciences and research, we are not going to have the people to get into the MARC programs and the other baccalaureate and post-baccalaureate programs. We feel this is a very good investment.

It may be late if anything to bring the high school students in to the research enterprise.

NCRR MINORITY PROGRAMS

Mr. STOKES. I am pleased with the increases that you have brought to our attention relative to this program and the other programs you referred to. What is the total amount of your budget?

Dr. WHITNEY. The entire budget is $319,151,000.

Mr. STOKES. In terms of programs that are targeted toward minorities, what percentage of that budget would you say these programs represent?

Dr. WHITNEY. About 10 percent.

RESEARCH CENTERS IN MINORITY INSTITUTIONS

Mr. STOKES. With regard to the RCMI program, other than the administrative flexibility for the Center For Research Resources, does moving the budget to the Center have any advantages for the RCMI program?

Dr. WHITNEY. We believe that it does. We are very pleased to be able to support that program. We are very pleased to have the Research Centers in Minority Institutions within the National Center for Research Resources. We believe that this change will enhance our work with Dr. McNairy and the RCMI program directors to continue to make this an expanding program.

The fact that our business is infrastructure fits very well with the mission of the RCMI.

Mr. STOKES. With regard to the previous answer of 10 percent, I would appreciate the record showing the amount of those minority programs.

[The information follows:]

National Center for Research Resources 1991 Request for Minority Programs

	Amount
Research Centers in Minority Institutions	$22,833,000
Minority High School Student Research Apprentice Program	8,500,000
Total	31,333,000

Mr. STOKES. Last year we recommended that the institutes co-fund RCMI institutions. To what extent has this occurred both within your organization and the other NIH institutes?

Dr. WHITNEY. Within the National Center for Research Resources we are exploring the cofunding of the medical RCMIs at Meharry, Drew and Morehouse as part of the General Clinical Research Centers program. The National Institute of Allergy and Infectious Diseases contributed $1,900,000 last year in cofunding of AIDS research, and will continue to contribute to our program.

We believe we also will be getting funds from the National Heart, Lung and Blood Institute for 1991. Cofunding with NIM organizations is continuing and growing.

HUMAN GENOME RESEARCH

Mr. STOKES. You stated that the RCMI program thrust will be expanded in order to enable RCMI institutions to participate in human genome research. Can you tell us what your plans are for the coming year in this area?

Dr. WHITNEY. There are a number of projects on-going at the RCMI's related to the human genome initiative. One center is working with Battelle Northwest in sharing technology to better define the human genome. That program has been on-going now for just about a year and is expanding to other centers.

We also will be receiving co-funding from the National Center for Human Genome Research for RCMI research. We are not sure how much money yet but we have been assured by them that they will co-fund some of our RCMI genome research.

CLINICAL TRIALS

Mr. STOKES. To what extent does NIH make use of RCMI funded institutions in clinical trials, especially for AIDS?

Dr. WHITNEY. There are a number of clinical trials going on in RCMI institutions. I mentioned Meharry; also Drew and Morehouse are participating with the research centers program on clinical trials on AIDS today. There will be more.

STAFFING FOR RCMI PROGRAM

Mr. STOKES. Along with the increase in your budget for the RCMI Program, have you increased the program staff or expanded it proportionately?

Dr. WHITNEY. Yes, we have doubled it in the past year, from two to four.

Mr. STOKES. Is this sufficient in terms of what this program does?

Dr. WHITNEY. Yes, sir, I think it is at this point in time. We need to get more experience with it.

CLINICAL ASSOCIATE PHYSICIAN PROGRAM

Mr. STOKES. How much is included in your request for the clinical research program to support the Minority Junior Physician and Dentist component?

Dr. WHITNEY. This year we have included within our GCRC budget $450,000 to support five minority Clinical Associate Physicians. This is in addition to the 45 traditional program CAPs and will allow the minority CAPs an additional three years of support if they wish to use it.

MINORITY HIGH SCHOOL PROGRAM

Mr. STOKES. The Minority High School Apprentice Program would receive an increase of $836,000 in the President's budget. This would bring the program from $1,800,000 to $2,600,000. How are you measuring the effectiveness of this particular program?

Dr. WHITNEY. It is difficult to do; many of the accounts of where these students go and how well they fare are anecdotal. We do know that a number of students who are supported in the MARC program and the MBRS program have been minority apprenticeship participants. We have also had several apprentices who scored very high in the Westinghouse Science Talent search.

We believe we have a high degree of success relative to the numbers of students in that program. For the investment, it is certainly worthwhile.

Mr. STOKES. Thank you.

Thank you, Mr. Chairman.

PRIMATE CENTERS RENOVATION

Mr. NATCHER. Doctor, you are requesting $3,000,000 for renovation of primate centers. Would the centers then meet animal laboratory accreditation standards?

Dr. WHITNEY. Yes, sir. Six of the seven centers are presently accredited by American Association for Accreditation of Laboratory Animal Care.

The problem is that with the vast increase in AIDS-related research we have come to the point where renovations of the facilities are simply not enough. We need construction to replace some renovated areas that have been taken up by AIDS research.

Mr. NATCHER. What will the total bill be for renovating the primate centers?

Dr. WHITNEY. I believe that if we had an additional $6,000,000, we could meet the current needs of the Private Centers. We would need $3,000,000 a year to maintain them.

USDA REGULATIONS

Mr. NATCHER. What is the status of the Department of Agriculture's animal facility regulations?

Dr. WHITNEY. Parts one and parts two of the regulations have become final. Those were in concert with our Public Health Service policy for the use and care of laboratory animals. Part three is still in draft form. There are some difficult areas having to do with psy-

chological well being of primates and exercise for dogs that must still be resolved.

If the regulations are finalized as initially published, it would be quite expensive to implement the necessary renovation and construction.

Mr. NATCHER. Would you give us an idea of estimated cost of compliance with the guidelines from the Department of Agriculture?

Dr. WHITNEY. I believe the economists at the USDA indicated it would be in the neighborhood of $1,000,000,000.

Mr. NATCHER. Last year Jane Goodall was here. She came by and visited me. At no time did she say to me that animals should not be used. She was very much concerned about animals being treated as humanely as possible. Doctor, we are too on this committee. We are in the same position now. Just treat them as humanely as possible, the animals that are being used. We are concerned about it.

Dr. Raub, I know you have been here all during the hearings. You know we are concerned about that.

Dr. Whitney, we want to thank you and your associates for appearing before our committee at this time in behalf of your budget request for fiscal year 1991.

It has been a good hearing. Thank you very much.

USE OF MAMMALS IN RESEARCH

Mr. Natcher. What percentage of NIH-funded research involves the use of mammals, particularly chimpanzees?

Dr. Whitney. The following table shows the various percentages of NIH-supported research involving animals:

System	Projects	%Total	Dollars	%Total
Mammals	17,836	45.3	$2,515,050,921	44.5
Humans	11,080	28.1	$1,423,458,286	25.2
"Other"	10,479	26.6	$1,708,238,091	30.2
Total	39,395		$5,646,747,298	
	Projects	%Total Mammals	Dollars	%Total Mammals
Rats/Mice	10,395	58.3	$1,475,959,726	58.7
Primates	1,194	6.7	$ 190,956,368	7.6

Mr. Natcher. Has this decreased over time?

Dr. Whitney. The use of mammals has shown a slight decrease in the past several years. We expect that trend to continue.

ACCREDITATION OF LABORATORY ANIMAL FACILITIES

Mr. Natcher. What percentage of NIH-funded institutions meet animal laboratory accrediting standards?

Dr. Whitney. NIH funds approximately 800 research institutions which utilize laboratory animals. Of these, approximately 300 institutions (37 percent) are accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC). However, all NIH funded institutions must file an animal welfare assurance statement with the NIH Office for Protection from Research Risks and be in compliance with PHS Guidelines for the Care and Use of Laboratory Animals. The reasons for an institution not being AAALAC-accredited are varied and the lack of such accreditation should not be construed to mean that the institution does not fully comply with the PHS guidelines.

BIOMEDICAL RESEARCH SUPPORT GRANTS

Mr. Natcher. How many Biomedical Research Support Grants were used for animal facility renovation in 1989?

Dr. Whitney. Expenditure data for 1989 will not be available for a few months. Data for 1988 show that approximately 25 percent of the BRSG awardees (154 out of 618) utilized some funds for support of animal facilities. A total of 3.2 percent (or $1.8 million) was allocated to upgrade animal facilities and to purchase

caging and related equipment in order that these institutions can comply with PHS policies on the humane care and treatment of animals.

SHARED INSTRUMENTATION

Mr. Natcher. What is the application response to the Shared Instrumentation (SIG) program each year?

Dr. Whitney. Over 400 SIG applications were received for funding in 1990, approximately the same number that were submitted in 1989. This represents a 45 percent increase in applications from previous years (1982-1988).

Mr. Natcher. How much funding have you distributed since the program began?

Dr. Whitney. After 8 years of operation the SIG Program has funded 1,029 applications for a total of $195.6 million.

Mr. Natcher. Will this be an on-going need?

Dr. Whitney. The recent surge in applications in both 1989 and 1990, which was nearly double that in earlier years, reflects the growing need for instrumentation in the $100,000 to $400,000 cost range. The rapid technological change in research instrumentation and the opening up of new research areas are the cause for the increased number of applications. The emergence of protein and genetic engineering and the development of new instruments such as adherent cell sorters and laser scanning confocal microscopes and the growing need to replace obsolescent equipment will continue to keep up the application pressure on this program.

RESEARCH CENTERS IN MINORITY INSTITUTIONS

Mr. Natcher. What are the eligibility requirements for Research Centers in Minority Institutions grants?

Dr. Whitney. An institution must have more than 50 percent minority student enrollment and award a doctoral degree in the health professions and/or a Ph.D. degree in the sciences related to health to be eligible to participate in the RCMI program. This program is available only to institutions within the United States and its territories.

Mr. Natcher. Are all eligible institutions funded each year?

Dr. Whitney. We have been able to provide RCMI support to all eligible applicants except one in recent years. There are currently no approved applications which have not been funded. The one eligible institution which has not been funded has failed to develop a meritorious application.

Mr. Natcher. How many years have these institutions received grants?

Dr. Whitney. Seven institutions have been funded continuously since 1985, the first year funds became available for the RCMI initiative. An additional eight institution received initial RCMI funds in 1986 and have been funded every year since then. In 1988, the grantee community was expanded from 15 to 17, the current number of RCMI-supported institutions, by initiating programs at two eligible universities.

Mr. Natcher. Does your funding initiative for the Research Centers in Minority Institutions program increase the number of grantees or the size of the awards?

Dr. Whitney. We are requesting a 30 percent increase in funding for the RCMI program in 1991. With this increase, we would be able to expand the number of grantees from 17 to 20; to increase the size of the grant awards for the most meritorious proposals, particularly for the study of AIDS, which has had a disproportionate impact on the minority community; and to facilitate the involvement of the RCMI grantees in the human genome initiative.

MINORITY HIGH SCHOOL PROGRAM

Mr. Natcher. Does the Minority High School Research Apprentice program provide stipends for its participants?

Dr. Whitney. Each apprenticeship slot is awarded at a level of $1,500. Students must be paid a salary. Each apprentice should receive a full-time research experience during the summer, preferably for 8 weeks or longer, but in no case less than 4 weeks. Salaries are at the prevailing scale for comparable work, but not less than the Federal minimum wage.

GENERAL CLINICAL RESEARCH CENTERS

Mr. Natcher. List the major areas of research conducted at the general clinical research centers.

Dr. Whitney. The array of research conducted at the general clinical research centers reflects the research missions of the several categorical institutes at NIH. The major research areas are immunology related, nutrition, sexually transmitted diseases, AIDS, rare diseases, maternal and child health, diabetes, heart-related diseases, cancer, digestive diseases, aging, and genetics-related.

NCRR INTRAMURAL PROGRAM

Mr. Natcher. Identify the major items of the Division of Research Services budget, which is funded through charges to the various Institutes' intramural research budgets.

Dr. Whitney. The major areas which are funded through charges to the various Institutes' intramural budgets are: Medical Arts and Photography; the NIH Library; Biomedical Engineering and Instrumentation; and Veterinary Resources.

LABORATORY ANIMAL SCIENCES AND PRIMATE RESEARCH

Mr. Natcher. Identify 1989-1991 funding for the major components of the Laboratory Animals Sciences and Primate Research Program.

Dr. Whitney. Following is a table showing funding for the major components of this program:

LABORATORY ANIMAL SCIENCES AND PRIMATE RESEARCH PROGRAM (LASPR)
(Dollars in Thousands)

Impact Data	1989 Actual	1990 Appropriation	1991 Estimate
Primate research centers	$36,505,000	$37,129,000	$37,541,000
Laboratory animal sciences	30,382,000	30,742,000	31,022,000
Total	66,887,000	67,871,000	68,563,000

CLINICAL TRIALS

Mr. Natcher. How many NIH-supported clinical trials are underway at the General Clinical Research Centers?

Dr. Whitney. There are over 80 clinical trials funded by various NIH components underway at the General Clinical Research Centers.

TRANSFER TO THE NATIONAL LIBRARY OF MEDICINE

Mr. Natcher. Why are you transferring $3.9 million in artificial intelligence grants to the National Library of Medicine in 1990?

Dr. Whitney. The task force on the reorganization of the Division of Research Resources (DRR) and the Division of Research Services (DRS) looked into alignment of the DRR's Biomedical Research Technology (BRT) program. The task force recommended that most of the BRT program remain with DRR, but that those grants related to data base development or artificial intelligence in medicine were more appropriate to the mission of the National Library of Medicine. Four grants and a total of $3.9 million were transferred in 1990.

AIDS ADVANCE

Mr. Conte. We understand that the resources developed and supported by the National Center for Research Resources provide the infrastructure so that research supported by the institutes can proceed. What is an example of an important advance in AIDS research which was made possible by one of your scientists?

Dr. Whitney. Various retroviruses which cause AIDS-like disease in nonhuman primates are under intense study at the Delta and New England Regional Primate Research Centers. Investigations at both of these Centers have demonstrated that immunization with a killed Simian Immunodeficiency Virus (SIV) vaccine prevented infection and disease in rhesus monkeys which had been experimentally exposed to the infectious SIV. All non-immunized (control) animals exposed to the same virus became infected with SAIDS and most animals have died. These successful vaccine development studies with SIV, which is very similar to human immunodeficiency virus (HIV), provide new hope that a vaccine for human AIDS is possible and can be successfully developed within the next several years.

GCRC NURSING SALARIES

Mr. Conte. The committee has heard that about 30 percent of the total GCRC costs are related to the salaries of research nurses at the centers. Are these salaries really increasing at 15 percent per year?

Dr. Whitney. Nursing salaries increased at a rate of about 15 percent per year between 1987 and 1989, and we assume that those salaries will continue to increase. We are now concerned that the salaries of other hospital based personnel will also increase to keep pace.

Mr. Conte. Is this true for both AIDS and Non-AIDS research?

Dr. Whitney. Yes, it is true that these increases occur both in AIDS and non-AIDS protocols.

Mr. Conte. What are you doing to meet this cost escalation?

Dr. Whitney. To meet this demand, each grant is carefully negotiated. Wherever possible, work is done using the less expensive outpatient methods, so that fewer nurses are required to be on duty around the clock.

GENERAL CLINICAL RESEARCH CENTERS

Mr. Conte. I understand that much of the clinical research conducted by NIH-supported investigators occurs in the General Clinical Research Centers. Without these centers, little clinical research could be accomplished. How does the network of clinical research centers work with other NIH extramural programs?

Dr. Whitney. The GCRCs interface with the other extramural programs by providing the needed clinical research infrastructure--beds, nurses, research dieticians, core laboratories, etc.--while the institutes provide the research support of the investigator--

salary, equipment, supplies, travel, etc. In other words, the GCRCs provide the quality environment which permits high quality clinical research.

Mr. Conte. How are the institutes' extramural staffs informed of the availability of GCRC resources to assist those programs?

Dr. Whitney. Interactions occur at NIH and at the grantee institutions. The NIH and ADAMHA have internal systems for announcing plans to develop certain research programs. GCRC program staff review these announcements, and where appropriate, contact institute staff to alert them to GCRC availability.

At the grantee institutions, GCRC program directors announce availability. Investigators who wish to conduct clinical research are usually aware of the resource at their or a neighboring institution.

TECHNOLOGY DEVELOPMENT

Mr. Conte. The committee has heard much about the Biomedical Research Technology Centers which your Center supports. How does the National Center develop these technologies in the first place?

Dr. Whitney. The resource Centers are investigator-initiated activities that are peer reviewed for scientific merit prior to funding by the National Center for Research Resources. Following successful review and assurance of the need for the technology, a new facility is approved for funding by NCRR for the entire research and development effort. In some cases, the basic science and engineering components have been supported by industry or by other government agencies (Department of Defense) as part of, for example, national efforts in high energy physics. NCRR also supports the development of biomedical applications of the new technology.

Mr. Conte. How is this activity related to your small grants, resource-related research projects, or Small Business Innovative Research grants?

Dr. Whitney. The small grants program supports pilot studies in high risk innovative areas of technology and engineering to demonstrate the feasibility of new approaches. These grants are available to both academic and commercial sector applicants. The resource-related research projects provide support for development of promising novel technologies in order to prepare them to be available in a resource center. The SBIR program supports the development of technologies by small business applicants. Successful SBIR applicants have previously received support through the small grants program. NCRR programs have been successful in transferring new technologies to the commercial sector.

Mr. Conte. How do you continue development of the technology once a center is established?

Dr. Whitney. All BRTP resource centers are required to have technology research and development as an essential component of their resource. Successful technologies that become readily

available and do not need further development for application to biomedical research problems are no longer supported by this mechanism.

PRIMATE RESEARCH CENTERS

Mr. Conte. Last year the directors of the Regional Primate Research Centers testified that core support in the centers has been decreasing over the past few years. Is this true?

Dr. Whitney. It is true that core support has not been increased in the 1991 request.

Mr. Conte. If this is true, what is the real effect on the ability of the Primate Research Centers to continue their programs of research?

Dr. Whitney. Inflationary increases in institutional salaries and other areas are decreasing the Centers' ability to maintain core support that is required to accommodate both the non-AIDS Center operations and the increasing number of AIDS research projects, and to maintain the number of animals needed for these many research projects.

Mr. Conte. In your professional judgment, what is needed to correct the situation?

Dr. Whitney. In my professional judgment, funding fully at the level of the National Advisory Research Resource Council recommendations could, if continued, provide a solution to this problem. In 1991, this would require an additional $6 million.

CHIMPANZEE BREEDING AND RESEARCH

Mr. Conte. The Committee is aware that your Center continues its chimpanzee breeding and research program. The program's goal is to assure the availability of chimpanzees for research in this country. In addition, it is our understanding that the Center is supporting the development of a colony of specific pathogen-free Rhesus monkeys for research on AIDS and hepatitis. What is the status of these two programs?

Dr. Whitney. The Chimpanzee Breeding and Research Program was established in September 1986 to create self-sustaining breeding colonies and provide support for research efforts to help preserve this species. This nationwide program was designed to bring the expertise of chimpanzee breeders and researchers together in a unified effort. There are currently 431 disease-free breeding chimpanzees in the program's five colonies. The breeding efforts have been very successful, with a total of 147 live births produced during the first three years of this program.

The Specific-Pathogen-Free (SPF) Rhesus Monkey Breeding and Research Program was initiated in September 1988 to create self-sustaining rhesus breeding colonies which are free from infection with simian retroviruses and herpes B virus. This is the first national effort to ensure the development of a stable population of SPF rhesus monkeys. There are six breeding colonies and two

research projects (behavior and genetics) in this total effort. The program is progressing well and will provide a dependable supply of high quality SPF rhesus monkeys for AIDS-related research and testing.

Mr. Conte. What are you doing to assure that these animals are raised, cared for, and used in the best possible circumstances?

Dr. Whitney. A national management committee for the Chimpanzee Breeding and Research Program includes representatives of the participating institutions as well as an ethicist and zoological park director. The management committee is responsible for developing standards to be followed by each participating institution and addressing questions of concern to the participants, the public and the government. Thus far, no chimpanzees have been issued for use in research.

Mr. Conte. Chimpanzees have been declared an endangered species. How can you justify using these animals for research?

Dr. Whitney. Only chimpanzees in the wild are considered endangered. Those bred and raised in captivity in the United States are not considered endangered, and the breeding program is actually contributing to the population of chimpanzees, since half of the animals produced will be returned to the breeding resources.

FUNDING INCREASE FOR INTRAMURAL PROGRAM

Mr. Conte. Your newly created center provides research resources to the intramural scientists at NIH. Funds to support those resources are provided by the institutes, centers, and divisions through the Management Fund and the Service and Supply Fund. Will these funding sources be increased sufficiently in 1991 to keep up with the 6.9 percent increase requested for NIH's intramural research mechanism?

Dr. Whitney. Sufficient obligation authority is requested for NCRR Management Fund and Service and Supply Fund activities to support the full level of NIH intramural research anticipated in 1991. Most of the NCRR increase is requested in the Service and Supply Fund where outlay is directly dependent on the level of actual institute requirements for services.

BIOMEDICAL RESEARCH SUPPORT GRANT FUNDED RESEARCH PROJECTS

Mr. Conte. For the record, please provide the committee with the numbers of research projects by disease category funded in 1989 through the BRSG program. What will be the impact of reduced funding levels in both FY 1990 and FY 1991?

Dr. Whitney. As requested, we are providing for the record the list of the numbers of research projects by disease category which were supported by the Biomedical Research Support Grant Program.

Assuming that the percentages of BRSG funds used by grantees in 1990 and 1991 will parallel those percentages in previous years, we can assume that about one-third of the funds will be used for pilot research and another one-third of the funds will be used for interim

and other support of on-going and regular research projects. In 1989 this amounted to an estimated $41.4 million for these research projects; in 1990, the estimate is $29.7 million; and in 1991, we estimate $8.8 million will be used for support of research projects.

Following is the list of numbers of research projects by disease as requested:

BIOMEDICAL RESEARCH SUPPORT GRANT PROGRAM
FY 1989 TRANS-NIH ISSUES AND OTHER RELEVANT SCIENTIFIC REQUESTS
ALPHABETICAL ORDER

SCIENTIFIC AREA	NCRR		
	DOLLARS	GRANTS	SUBPROJECTS
AGING RESEARCH	883,229	145	226
ALZHEIMER'S DISEASE RESEARCH	83,201	21	23
ANEMIA RESEARCH	101,614	20	20
ARTHRITIS RELATED RESEARCH	777,539	105	160
ASTHMA RELATED RESEARCH	28,149	10	10
ATHEROSCLEROSIS RELATED RESEARCH	143,675	17	21
BEHAVIOR RELATED RESEARCH	4,012,778	272	1065
BIOTECHNOLOGY DIRECT & RES BASE	15,985,804	434	2560
BIOTECHNOLOGY DIRECT RESEARCH	8,934,829	370	1444
CANCER RESEARCH	3,835,671	229	583
CHOLELITHIASIS & GALLBLADDER DISORDERS	76,560	10	12
CHROMOSOME MAPPING & DNA SEQUENCING	4,273,953	270	666
CHRONIC LIVER DISEASE & CIRRHOSIS RES	63,402	12	13
CHRONIC OBSTRUCTIVE PULMONARY DIS RES	55,728	4	5
CONGENITAL ABNORMALITIES RESEARCH	1,252,501	163	258
CYSTIC FIBROSIS RELATED RESEARCH	19,686	10	10
DIABETES AND DIABETES RELATED RESEARCH	923,222	121	180
DIAGNOSTIC RADIOLOGY RESEARCH	479,384	76	116
DIGESTIVE DISEASES RESEARCH	1,873,554	163	306
DRUG DEVELOPMENT RESEARCH	1,259,123	161	234
EPSTEIN BARR VIRUS RESEARCH	79,449	8	9
GENETICS RELATED RESEARCH	6,859,304	326	1068
HEAD INJURY RESEARCH	23,267	10	10
HEART RESEARCH	2,639,957	221	557
HEMOCHROMATOSIS RESEARCH	111	1	1
HEPATITIS RESEARCH	62,682	12	12
HERPES RESEARCH (GENITAL AND OTHER)	120,692	18	18
HUMAN CHROMOSOME MAP & DNA SEQUENCING	540,829	73	103
HYPERTENSION RELATED RESEARCH	514,300	71	99
IMMUNOLOGY RELATED RESEARCH	4,470,755	283	797
IMMUNOTOXICOLOGY RESEARCH	23,376	5	5
INTERNATIONAL HEALTH RESEARCH	69,500	18	21
INTERSTITIAL CYSTITIS RESEARCH	496	1	1
KIDNEY RELATED RESEARCH	549,920	74	110
LEPROSY RESEARCH	12,981	4	4
LOW BIRTH WEIGHT & INFANT MORTALITY	188,449	31	34
LUPUS ERYTHEMATOSUS RESEARCH	80,214	11	12
LYME DISEASE RESEARCH	33,440	6	7
MATERNAL AND CHILD HEALTH RESEARCH	2,567,933	241	571
MENTAL RETARDATION RESEARCH	55,642	19	20

MINORITY HEALTH RESEARCH	316,080	70	103
NATIONAL TOXICOLOGY PROGRAM	2,076,485	223	438
NEPHRITIS, NEPHROTIC SYND, NEPHROSIS	32,715	7	9
NUTRITION RELATED RESEARCH	1,210,203	156	283
NUTRITIONAL DEFICIENCY RESEARCH	31,925	13	13
OSTEOPOROSIS RESEARCH	194,101	27	33
PARKINSON'S DISEASE RELATED RESEARCH	80,702	18	19
PERINATAL CONDITIONS RESEARCH	130,193	24	25
PERTUSSIS RELATED RESEARCH	21,239	2	2
PNEUMONIA AND INFLUENZA RESEARCH	133,922	19	23
POPULATION RELATED RESEARCH	1,521,169	159	310
PREVENTION & PREVENTION RELATED RES	3,450,824	292	833
RARE DISEASE RESEARCH	2,137,185	228	439
REHABILITATION RELATED RESEARCH	1,421,165	187	379
SEXUALLY TRANSMITTED DISEASE RESEARCH	320,208	49	56
SICKLE CELL DISEASE RESEARCH	28,202	7	7
SLEEP RELATED RESEARCH	96,582	31	35
SMOKING AND HEALTH RELATED RESEARCH	141,968	29	34
SPINAL CORD INJURY & REGENERATION RES	184,903	29	31
SUBSTANCE ABUSE RESEARCH	598,724	102	147
SUDDEN INFANT DEATH SYNDROME RESEARCH	21,199	3	3
TRANSPLANTATION RESEARCH	921,460	90	130
TREATMENT OUTCOME RESEARCH	547,745	50	63
TROPICAL DISEASE RESEARCH	357,341	58	71
ULCERS OF THE STOMACH AND DUODENUM	12,374	3	3
ULTRAVIOLET RADIATION RESEARCH	222,706	41	54
VACCINE DEVELOPMENT RESEARCH	192,596	31	38

MINORITY HIGH SCHOOL PROGRAM

Mr. Conte. Your Minority High School Student Research Apprentice program has been supporting students since the early 1980s. What research activities are these students involved in?

Dr. Whitney. The students in the Minority High School Student Research Apprentice program (MHSSRAP) take part in a wide range of scientific research. They are involved in whatever research is being conducted by the institutions which employ them.

Mr. Conte. What are your plans for this program in the coming fiscal year?

Dr. Whitney. Through 1989 over 8,000 minority high school students have been supported through this important program whose mission is to attract students to potential careers in biomedical research and health professions. In 1990, we will provide support to some 2,144 minority high school students because several other institutes and centers at NIH have agreed to provide additional funding for this program. In addition to NCRR's appropriation of $1,810,000 the other NIH institutes and centers have provided $882,000. The National Institute of Mental Health has contributed $225,000, and NCRR will add $300,000 from other programs for a grand total of $3,217,000.

In 1991 we anticipate being able to support 1,764 high school students with the funds specifically requested for this program. With the funds redirected from the BRSG program ($5.9 million), the MHSSRAP will support 5,100 students.

GENERAL CLINICAL RESEARCH CENTERS

Mr. Smith. What was the Council's ceiling for 1990 and the 1990 appropriation for the General Clinical Research Centers Program?

Dr. Whitney. The Council ceiling for the GCRC sites funded in 1990 was $125 million for direct costs. Indirect costs would add $10 million for a total of $135 million. The 1990 appropriation for the GCRCs was $115,284,000.

Mr. Smith. What is the projected Council ceiling for 1991?

Dr. Whitney. The projected Council ceiling for GCRC sites funded in 1990 for 1991 is $132 million for direct costs.

Mr. Smith. Does the projected ceiling for FY91 include indirect costs?

Dr. Whitney. No, it does not.

Mr. Smith. What are the indirect costs?

Dr. Whitney. Indirect costs in 1991 are projected to be $10.6 million.

Mr. Smith. How reliable has the Council ceiling been in predicting actual future costs for the GCRC program?

Dr. Whitney. The Council recommended ceiling has been within 1-2 percent of actual future costs of the GCRC program over the previous 5 years.

Mr. Smith. What impact will the President's budget request (which shows no increase in funding for the Clinical Research Centers) have on the a) number of centers; b) number of young investigators who will not be supported; c) programs in cancer, atherosclerosis and AIDS which might be suspended?

Dr. Whitney. If nursing salaries continue to increase at an annualized rate of 15 percent (with those salaries accounting for 30 percent of the entire centers budget) and if hospital-based research costs (which account for 40 percent of the entire GCRC budget) continue to increase at the current rate of about 20 percent per year, several centers may be closed. Every effort will be made to maximize resource utilization at GCRC sites. Funding of young investigators with meritorious grant applications to the Clinical Associate Physician Program will continue to receive the highest program priority; it is imperative that gifted young physician and dentist investigators continue to develop the clinical research skills to become the independent clinical investigators of the future. Other young investigators at GCRC sites that may need to be closed will not have that opportunity. The network of GCRCs provides the clinical research infrastructure for investigators who receive their primary research support from the disease-oriented institutes at NIH; if fewer centers are to be funded in 1991, or if inpatient and outpatient resources are limited because of fiscal constraints, fewer studies will be carried out. Since clinical

research studies of cancer, atherosclerosis and AIDS are among the most common research areas across the network of GCRCs, research in those important areas will be reduced.

Mr. Smith. What budget increase will be necessary to maintain the GCRC program at their current level of support - including the crucial support of young investigators in the Clinical Associate Physician programs?

Dr. Whitney. A budget increase of $26 million would be needed for 1991 to maintain the GCRC program at the current level of support in view of the projected rates of increases for research nursing salaries and other hospital-based research costs.

RESEARCH CENTERS IN MINORITY INSTITUTIONS

Mr. Stokes. This committee also asked NIH to consider including RCMI awards as part of the formula that is used to determine the eligibility and level of support for the Biomedical Research Support Grant. Will this be implemented?

Dr. Whitney. RCMI awards are not currently eligible for Biomedical Research Support Grants. This policy has been reviewed and the NCRR will recommend at the next meeting of the National Advisory Research Resource Council in June, that RCMI awards be included in determining BRSG eligibility, the same as other center grants.

BIOLOGICAL MODELS AND MATERIALS RESEARCH

Mr. Dwyer. In recent years, much attention has been focused on the role of animals in biomedical research. While we all must realize the important role that animal research has played, and will continue to play in the future, it is very important for us to explore nonmammalian models. The Biological Models and Materials Resources Program (BMMRP) is the focal point for the development of nonmammalian models at the NIH. Are there any programs operated by universities or private institutions which are also involved with developing nonmammalian models? Does BMMRP work with these institutions on a regular basis?

Dr. Whitney. The BMMRP has actively worked with several institutions to promote the use of nonmammalian models in biomedical research. Currently the BMMRP funds the Center for Alternatives to Animal Testing (CAAT) at the Johns Hopkins University which is a focus for the development of in vitro toxicity testing methodologies and a mechanism to disseminate research progress in this area. The BMMRP regularly communicates with and participates in activities of the Tufts Alternative Program which is part of Tufts University Center for Animals and Public Policy. Last year, the BMMRP participated in an advisory meeting to establish the University of California Program Center for Animal Alternative Methods.

Mr. Dwyer. The budget justification states that the BMMRP supports several resource centers that acquire, maintain, and distribute a varied number of lower organisms to the research community. Is there a charge associated with this program?

Dr. Whitney. Resources, such as the American Type Culture Collection, the Yeast Genetic Stock Center, and the Caenorhabditis Genetics Center which are supported by BMMRP, charge investigators a modest fee, in most cases only shipping and handling. The National Disease Research Interchange which provides human tissues and organs, and the MIT Cell Culture Center which provides large scale production of animal cells, charge researchers a service fee for the retrieval, preservation and delivery of tissues, or for consumable materials, respectively. All of the fees associated with these centers are used by the centers to reduce the cost to the government.

Mr. Dwyer. The budget justification states that the centers supported by the BMMR will be indispensable to investigators involved in the human genome project. As Dr. Watson has stated that the human genome project will begin in earnest this year, why have you requested $5.356 million for fiscal year 1991, a decrease of $8,000 from fiscal year 1990 appropriations?

Dr. Whitney. The NIH policy in regard to the 1991 budget was to request increases in AIDS, the National Center for Human Genome Research (NCHGR) and the NIH Minority Programs. Most other programs, including BMMR, were maintained at the 1990 level.

The NCRR is investigating the possibility of having the NCHGR cofund some of the activity in this area as it pertains to genome research.

GENERAL CLINICAL RESEARCH CENTERS

Mr. Early. For FY91, the General Clinical Research Centers Program is increased by only $798,000. Is this increase sufficient to maintain the same level of activity in 1991 as in 1990?

Dr. Whitney. The $798,000 increase in the 1991 General Clinical Research Centers Program budget is to cover the projected increase for AIDS-related research. The 1991 GCRC budget for non-AIDS research is level. Nursing salaries, which make up 30 percent of the entire budget, increased at an annualized rate of 15 percent from 1987 to 1989, and hospital-based research costs, which account for 40 percent of the GCRC budget, increased at an annual rate of 21 percent in 1989. If this trend continues, the General Clinical Research Centers will not operate at the same level of activity in 1991 as in 1990.

Mr. Early. Will this cover the full cost or does this assume a downward negotiation and, if so, of what magnitude?

Dr. Whitney. The President's 1991 Budget assumes downward negotiations of approximately 20 percent.

Mr. Early. How much did the cost of conducting clinical research increase in FY89 and what are your projections for FY90? FY91?

Dr. Whitney. Relative to 1988, the cost of operating the General Clinical Research Centers Program increased from $102,762,000 to $108,556,000 in 1989. In 1990, the Council recommended operating level for the Program is approximately $125 million direct costs. Since indirect costs average 8 percent of total direct costs, it would require $135 million to fund existing Centers with no downward negotiations. Based on preliminary information, we project that the Council's recommended ceiling for GCRC sites funded in 1990 will be approximately $132 million direct costs in 1991. Indirect costs will add another $10.6 million. Therefore, $142.6 million would be required to fund these Centers in 1991, without downward negotiation.

Mr. Early. How much of its increased costs will each center be expected to absorb in FY90 and FY91?

Dr. Whitney. To decrease the average level absorbed in 1990, three Centers were closed. The remaining Centers must absorb approximately 16 percent of their clinical research costs.

Mr. Early. What was the NCRR budget request for the General Clinical Research Centers Program, and how does it differ from the request before us?

Dr. Whitney. The NCRR budget request to NIH for the General Clinical Research Centers was $162,275,000. The 1991 President's Budget is $116,082,000 a difference of $46,193,000.

Mr. Early. Doctor, what is the Council ceiling and the FY90 allocation for the General Clinical Research Centers Program?

Dr. Whitney. The Council ceiling for 1990 is $125 million for direct costs. Indirect costs would add another $10 million, for a total of $135 million. The 1990 allocation is $116 million for the General Clinical Research Centers Program.

Mr. Early. What is the projected council ceiling for FY91?

Dr. Whitney. The projected Council ceiling for 1991 is $132 million for direct costs.

Mr. Early. And does that include indirect costs?

Dr. Whitney. That does not include indirect costs. Indirect costs amount to about $10.6 million.

Mr. Early. Doctor, last year, you indicated that the nursing crisis and salary improvements for nurses have a measurable impact on the GCRC Program and budgets. In 1988, nurses salaries went up about 16%. What was the increase in 1989?

Dr. Whitney. The nursing crisis and salary improvements continue to put a great deal of pressure on the GCRC Program. Nursing salaries continue to rise at an annualized 15 percent rate.

Mr. Early. Since nurses account for approximately 60% of all FTE's supported through this program, what impact has the relatively flat federal funding had on GCRC operating budgets and programs?

Dr. Whitney. As a result of the relatively flat federal funding, three fewer Centers will be funded in 1990 and the remaining funded Centers must absorb an average of 16 percent of their projected costs by either reducing their research activity or obtaining funds to support their clinical research activities from other sources.

GENERAL CLINICAL RESEARCH CENTERS

Mr. Early. How many research beds will be supported in FY90 and FY91, and how does this compare with prior years?

Dr. Whitney. The research beds of the GCRCs accommodate both inpatient and outpatient research activities. In considering clinical research support to Centers, numbers of research inpatient days and outpatient visits determine the configuration of a Center. Since outpatient visits include prolonged studies of up to 14 hours, inpatient beds are often used to accommodate outpatient visits. In 1990, we project that there will be 115,000 inpatient research days and 210,000 outpatient visits. In 1991, we project that there will be 100,000 inpatient research days and approximately 215,000 outpatient visits.

Mr. Early. And what would these figures be exclusive of beds for AIDS research?

Dr. Whitney. The figures above include AIDS research, which represents approximately 20 percent of inpatient and outpatient research activity .

Mr. Early. Doctor, to what extent is research activity at the General Clinical Research Centers continuing to increase?

Dr. Whitney. In 1985, the distributed national network of Centers hosted 3,675 research projects carried out by 4,398 investigators who received $291.8 million of research funding from the other components of NIH. In 1989, the Centers hosted 4,608 research projects carried out by 7,256 investigators who received $544.4 million of primary research funding from the other components of NIH. In addition, investigators received another $150 million from other federal, state, and private sector sources for primary research funding.

Mr. Early. What about in the non-AIDS area?

Dr. Whitney. The data above represent both AIDS and non-AIDS. On the average, about 80 percent of research projects are non-AIDS; although that proportion has diminished slightly since 1985.

Mr. Early. How many GCRCs are now involved in AIDS research?

Dr. Whitney. Fifty-two Centers are involved with AIDS research. Twelve of these 52 are involved in pediatric AIDS research.

Mr. Early. Is AIDS research continuing to affect the allocation of GCRC resources for non-AIDS research?

Dr. Whitney. AIDS research continues to increase across the national network of GCRCs. The GCRCs are an important interface for investigators funded by NIAID and NICHD to carry out clinical trials of treatments for AIDS associated with adult and pediatric studies of the AIDS Clinical Trial Group. Non-therapeutic AIDS research is also carried out at GCRCs. Resources for AIDS research are increasing while those for non-AIDS are level.

Mr. Early. To what extent?

Dr. Whitney. Support for AIDS research is carefully monitored so that non-AIDS research can continue.

Mr. Early. What did NCRR request for the General Clinical Research Centers program?

Dr. Whitney. NCRR's request to NIH for the General Clinical Research Centers was $128,222,000 for non-AIDS and $34,053,000 for AIDS for a total of $162,275,000.

DOWNWARD NEGOTIATIONS

Mr. Early. Doctor, what percent of downward negotiations will be required in your other four programs in FY 91?

Dr. Whitney. The percent of downward negotiations which will be required for NCRR's other centers programs are as follows:

Biomedical Research Technology Program.....	20.0%
Research Centers in Minority Institutions.....	5.0%
Biological Models and Materials Research.....	13.2%
Laboratory Animals Sciences and Primate Research...	13.2%

Mr. Early. Will you have to terminate any ongoing activities?

Dr. Whitney. The current program will be maintained as a result of the downward negotiations, although in the case of Biomedical Research Technology Program, the number of centers supported may have to be reduced.

BIOMEDICAL RESEARCH TECHNOLOGY

Mr. Early. No increase is recommended for the BRT program in FY 91. What impact will this have on BRT activities?

Dr. Whitney. Level funding will necessitate postponement of new activities, particularly in new or ongoing centers that have recently been competitively reviewed. Some ongoing activities will be reduced, to accommodate normal increases in costs of conducting research. The alternative is to decrease the number of grants, and that will also be considered.

Mr. Early. What is the downward negotiation for the BRT program, and what effect is it having on the BRT program, particularly the centers program?

Dr. Whitney. The downward negotiation for the Biomedical Research Technology centers program in 1991 is 20 percent below estimated council recommended ceiling. An additional $8,022,000 would be needed to fully fund the BRTP centers.

Mr. Early. Doctor, in your professional judgment, what we <u>should</u> be doing in this area?

Dr. Whitney. Opportunities have never been better for application of advances in the physical and engineering sciences to biomedical research. The emerging technologies offer unprecedented power--both in speed and in resolution of microscopic fine structure--for studying biological systems. These technologies are increasingly expensive, more so than the technologies with which NCRR has customarily dealt. An increase of approximately $15 million would be needed to begin to develop and support shared resources in these new technologies in 1991.

Mr. Early. What was NCRR's original request for this program?

Dr. Whitney. NCRR's request to NIH for the BRTP was $66,857,000.

Mr. Early. What priorities would NCRR pursue if additional resources were available for this program?

Dr. Whitney. Additional resources would be divided between supporting new initiatives and fully funding existing resource centers. New initiatives in biomedical technology which would be pursued include whole body magnetic resonance imaging instrumentation at high fields, biomedical beam lines at the new synchrotron light sources at the Department of Energy's National Laboratories, biomedical application of large scale parallel computing, and biomedical research utilization of the free electron laser. Several of these initiatives will require funding commitments within the next year if biomedical researchers are to obtain access to the new technologies involved. All existing resource centers are being funded well below approved levels for 1990; additional resources would make possible less severe reductions in 1991.

BIOTECHNOLOGY TRAINING

Mr. Early. Bring us up to date on the progress that has been made in providing training opportunities in biotechnology resources.

Dr. Whitney. Although no new training opportunities have been initiated, an active training program continues in the Biomedical Research Technology Program. This is conducted in a variety of ways including on site training of students and postdoctoral fellows as well as other users of the resources. In addition, many resources conduct workshops either at the resource site or at professional meetings. Approximately $1.2 million of resource funding was dedicated to training activities in 1989. Approximately $900,000 will be devoted to training in 1990. In addition, BRTP has awarded grants for symposia or conferences that have training components as part of the program. Training in supercomputer use has been given special priority for the past three years by BRTP with a cooperative agreement designed to train biomedical investigators in use of supercomputers for their research projects. Approximately $846,000 was awarded specifically for supercomputer training activities in 1989. The amount to be awarded for 1990 for this activity is uncertain and under review at the present time.

Mr. Early. What are your plans for FY 91?

Dr. Whitney. An emphasis in 1991 will be on the training of minority investigators to increase their utilization of BRTP resources. This will be accomplished by support of collaborative projects between minority investigators and BRTP resources. Another area of emphasis will be in the training of investigators for research on in vivo magnetic resonance imaging and spectroscopy. Emphasis will be placed upon training of radiologists in areas of basic research.

Mr. Early. What resources have been allocated for this program in FY 91?

Dr. Whitney. No new funds are available to support these new directions in training. These new training initiatives will have to be absorbed by means of a redistribution of existing resources.

PRIMATE RESEARCH CENTERS

Mr. Early. What remains to be done with regard to the systematic upgrading and renovations at the primate research centers?

Dr. Whitney. The seven regional primate research centers require additional laboratory space and biosafety containment facilities to conduct AIDS-related research involving infectious agents, such as the human immunodeficiency virus (HIV); repairs and maintenance of existing facilities; caging replacement to meet USDA regulations related to improving the psychological well-being of nonhuman primates; and the continued replacement of obsolete equipment items.

Mr. Early. What is the current cost estimate for completing the upgrading and renovations?

Dr. Whitney. Based on current construction and facility renovation costs, an estimated $8.0 million to $10.0 million annually will be required for a period of four to five years to complete the necessary upgrading and renovations of the seven regional primate research centers' facilities.

Mr. Early. What is the cost estimate for meeting the revised PHS Animal Welfare Policy?

Dr. Whitney. In 1989 it was estimated that compliance of the seven regional primate research centers with the proposed revisions of the PHS Animal Welfare Policy that will result from the new USDA regulations, Parts I, II, and III, would cost $75 million. These estimates involve a considerable amount of construction to create additional space for housing of primates.

Mr. Early. What is the estimate for regular annual maintenance to maintain standards?

Dr. Whitney. To maintain appropriate standards, the repair, upkeep, and general maintenance of facilities at the seven regional primate research centers will continue to require a minimum of $3.0 million annually.

Mr. Early. Doctor, how much did NCRR request of NIH for primate center repair and renovation in FY 91? What was the NIH request to the PHS?

Dr. Whitney. NCRR's request to NIH for primate research center repair and renovation in 1991 was $3,000,000.

The NIH request to PHS was submitted in aggregate. The repair and renovation figure for the Primate Research Center was not broken out as a separate item.

Mr. Early. How much is available for core support for the primate centers, and how does this compare with the FY 90 and FY 89 levels of support?

Dr. Whitney. The 1991 budget request for core support of Primate Research Centers is $25,473,000, the same as 1990. The 1989 actual was $25,578,000, a difference of $105,000.

Mr. Early. How much did NCRR request of NIH for primate centers exclusive of repair and renovation funds?

Dr. Whitney. The NCRR request to NIH for the Primate Research Centers, exclusive of repair and renovation funds, was $43,849,000.

EXTRAMURAL ANIMAL FACILITIES

Mr. Early. How many applications do you anticipate receiving and funding under the extramural animal facilities improvement program in FY 90 and 91?

Dr. Whitney. In 1990, 119 applications have been received for the extramural animal facilities improvement program. We anticipate funding approximately 45 (44 percent) of the 103 applications that are expected to be approved by the Council for funding. The projected figures for 1991 are similar.

Mr. Early. What is the backlog of approved but unfunded applications? Is it growing, declining, or has it remained relatively constant?

Dr. Whitney. The number of approved, but unfunded applications, continues to grow. Each year new institutions apply for assistance. Other institutions that have completed an initial phase of a large improvement program may apply again for funds to complete a second phase. Reapplications are also received from institutions that did not successfully compete for funds in previous years. We expect the total of unfunded applications in 1990 to be approximately 60.

NCRR PRIORITIES

Mr. Early. If an increase over the FY91 request is provided for NCRR, how would you use these additional funds? What would your priorities be?

Dr. Whitney. If an increase in funds for 1991 was provided by Congress, the additional funds would first be used to fund 20 more approved unfunded research projects grants in the Biological Models and Materials Research Program. Next, we would add funds to reduce downward negotiations in the centers supported by NCRR to not more than 10 percent. Then we would provide for a small increase in core support to the Primate Research Centers. Then we would restore the Biomedical Research Support Grant (BRSG) program to the 1990 level. Further additional funds would be utilized to fully fund the centers of the various programs at council recommended levels. We would also fund a small number of research project grants in Biomedical Research Technology and Laboratory Animal Sciences. Our next priority would be to bring the BRSG program to a level of $60 million. We would also add funds to expand support to the Research

Centers in Minority Institutions. The small grants program, the shared instrumentation grant program, and the animal facilities improvement program would also be increased. Finally, we would request funds to support construction of new clinical, laboratory, and animal facilities necessary for the conduct of biomedical research, both AIDS and non-AIDS.

LOSS OF OPPORTUNITIES

Mr. Early. Will any significant new research initiatives or opportunities be lost or delayed by lack of funds in the FY91 budget?

Dr. Whitney. Yes, there are several new research opportunities which will be delayed due to a lack of funds in the 1991 budget.

Mr. Early. Please provide, for the record, a list of these along with a brief descriptions and the funding requirements associated with each.

Dr. Whitney. A list of new initiatives which would be delayed is as follows:

New research project grants in LASPR for animal models, intercurrent lab animal diseases and transgenics; in BRT for pre-resource research; and in BMMR in the area of alternatives and models, would cost an additional $7,550,000.

Four new Biomedical Research Technology (BRT) Centers could be started in fields critical to the progress of biomedical research. These include opportunities in in vivo magnetic resonance imaging (MRI) and spectroscopy.

Other new opportunities include resource centers in complex carbohydrates and flow cytometry techniques, both important in underpinning the rapidly expanding biotechnology research effort; the use of biomedical computing; and new synchrotron light sources. These opportunities could be initiated for about $15,000,000.

Approximately $10,000,000 could add five new General Clinical Research Centers, and the beds, nurses and other patient-oriented research resources needed to meet demands for clinical studies.

About $5,225,000 would allow the start-up of two new Laboratory Animal Sciences Diagnostic Centers and six new Biological Models and Materials Research (BMMR) Centers, including two for aquaculture. These centers are geared toward improving the health of research animals, or reducing the number of research animals used in research. A $1,000,000 small grants program could be initiated within the Laboratory Animal Sciences Program (LASPR) to increase support for innovative research in this area.

New funds in the amount of $90,000,000 would support Research Facilities Improvement to help address the deterioration of the research facility infrastructure. Of this amount, $15,000,000 would be targeted for minority institutions.

REDUCTIONS IN SCOPE

Mr. Early. To what extent will there be major reductions in the scope of ongoing or new initiatives because of the FY91 funding levels?

Dr. Whitney. There will be no major reductions in the scope of ongoing initiatives in NCRR's programs, other than in the Biomedical Research Support Grant (BRSG) program, due to the 1991 funding levels.

Mr. Early. For the record, please provide a list of these along with a brief description and the amounts associated with each initiative.

Dr. Whitney. The Biomedical Research Support Grant program awarded $44,385,000 to 653 grantees in 1990. The program, which provides the only flexible federal funding for biomedical research, provides for over 9,000 small research projects, opportunities for interim support, central resource renovation, and support for new or young investigators will be funded at $11,800,000 in 1991, a reduction of $32,585,000 from 1990.

BIOMEDICAL RESEARCH SUPPORT GRANTS

Mr. Early. Doctor, you are proposing to restructure the Biomedical Research Support Grant (formula) program. Are there any other programs where funds can be used for pilot studies to support innovative and unorthodox research ideas?

Dr. Whitney. The BRSG program is the major source of funding for new and unusual ideas and for supporting young investigators; several other Institutes provide funding for small research grants for discrete innovative projects.

Mr. Early. To support pilot projects of new, young faculty members?

Dr. Whitney. Some large medical schools may have discretionary funds to use for the purpose of supporting pilot projects of young faculty members, but medium and small size institutions generally do not have this flexibility.

Mr. Early. For interim support to maintain continuity of meritorious research programs?

Dr. Whitney. The BRS formula grant program is the only source of funding that we are aware of that allows institutions the flexibility to provide for the continuity of meritorious research programs.

Mr. Early. For central resources to support shared core facilities?

Dr. Whitney. The BRSG program is the only source of funding that we are aware of that allows institutions the flexibility of using the funds for central resources to support shared core facilities.

Mr. Early. How many institutions will be affected by this change, and what impact will this change have, in general?

Dr. Whitney. Approximately 650 institutions will receive BRSG grants in 1991. They will all be affected as the size of their grants will range between $5,000 and $30,000. The upper limit is considerably lower than the maximum award of $258,000 in 1990. In 1991, the average BRSG will be approximately $17,000, compared to an average of approximately $70,000 in 1990.

PROGRAM FUNDING IN CONSTANT DOLLARS

Mr. Early. Provide for the record what the proposed FY 91 funding level for the GCRC, BRT, and LASPR programs would be in terms of constant dollars (using 1980 dollars).

Dr. Whitney. The 1991 funding level in 1980 constant dollars for the following programs is:

	1991 Request	1980 Constant Dollars
Clinical Research	$116,857,000	$55,422,000
Biomedical Research Technology Prog.	40,017,000	18,996,000
Laboratory Animal Sciences and Primate Research	68,563,000	32,547,000

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Research Resources

FY 1991 Budget

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NATIONAL INSTITUTES OF HEALTH

Research Resources

For carrying out section 301 and Title IV of the Public Health Service Act with respect to research resources and general research support grants, [$354,191,000] *$319,151,000*: Provided, That none of these funds [, with the exception of funds for the Minority Biomedical Research Support program,] shall be used to pay recipients of the general research support grants program any amount for indirect expenses in connection with such grants.

(Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 1990.)

NATIONAL INSTITUTES OF HEALTH

RESEARCH RESOURCES

Amounts Available for Obligation 1/

	1989 Actual	1990 Appropriation	1991 Estimate
Appropriation	$362,987,000	$354,191,000	$319,151,000
Enacted administrative reduction	-4,379,000	-457,000	---
Subtotal, adjusted appropriation	358,608,000	353,734,000	319,151,000
Real transfer to the Health Resources and Services Administration for AZT grants	-532,000	---	---
Comparative transfer to:			
Fogarty International Center for Passport Function	-3,000	-3,000	---
National Library of Medicine for Artificial Intelligence in Medicine Grants	-3,615,000	-3,875,000	---
National Institute of General Medical Sciences for Minority Biomedical Research Support	-29,199,000	-30,254,000	---
Comparative transfer for administrative costs of the Research Centers in Minority Institutions Program from:			
National Cancer Institute	+49,000	---	---
National Heart, Lung, and Blood Institute	+34,000	---	---
National Institute of Dental Research	+ 4,000	---	---

	1989 Actual	1990 Appropriation	1991 Estimate
National Institute of Diabetes, and Digestive and Kidney Diseases	+18,000	---	---
National Institute of Neurological Disorders and Stroke	+18,000	---	---
National Institute of Allergy and Infectious Diseases	+24,000	---	---
National Institute of General Medical Sciences	+23,000	---	---
National Institute of Child Health and Human Development	+13,000	---	---
National Eye Institute	+ 7,000	---	---
National Institute of Environmental Health Sciences	+ 7,000	---	---
National Institute on Aging	+ 7,000	---	---
National Institute on Arthritis and Musculoskeletal and Skin Diseases	+ 5,000	---	---
National Center for Nursing Research	+ 1,000	---	---
John E. Fogarty International Center	+ 1,000	---	---
National Library of Medicine	+ 2,000	---	---
Comparative transfer from: The Office of the Director, NIH, for cost of increase in FTE	+114,000	---	---
The Office of the Director for the Research Centers in Minority Institutions	+15,312,000	+17,503,000	---
Subtotal, adjusted budget authority	340,898,000	337,105,000	319,151,000
Unobligated balance, start of year	+23,935,000	---	---
Unobligated balance, end of year	---	---	---
Unobligated balance, lapsing	-77,000	---	---
Total, obligations	364,756,000	37,105,000	319,151,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: FY 1989 -- $16,785,000 FY 1990 -- $18,066,000; and FY 1991 -- $2,340,000.

NATIONAL INSTITUTES OF HEALTH

Research Resources

Budget Mechanism
(Dollars in thousands)

	1989 Actual		1990 Appropriation		1991 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research grants:						
Research projects:						
Noncompeting					4	$787
Admin. suppl						
Competing						
Renewal						
New			4	$749		
Supplemental						
Subtotal competing			4	749		
Subtotal, res. proj			4	749	4	787
Research Centers:						
Clinical research	78	$107,474	78	115,284	78	116,082
Biomedical research technology	60	34,845	59	32,074	59	32,087
Laboratory animal sciences and primate research	47	47,996	47	49,091	47	49,701
Biological models and materials research	4	615	6	1,342	6	1,342
Research centers in minority institutions	17	15,312	17	17,503	20	22,833
Subtotal, research centers	206	206,242	207	215,294	210	222,045

Other research:						
Research career programs.....	9	538	9	559	9	561
Biomedical research support....	775	88,762	790	78,788	810	52,966
Other research related.....	131	22,389	129	22,574	129	22,635
Subtotal, other research...	915	111,689	928	101,921	948	76,162
Total, research grants.....	1,121	317,931	1,139	317,964	1,162	298,994
Training:						
Individual awards:						
Noncompeting.....	3	91	4	93	4	93
Competing:						
New.....	--	--	2	40	2	40
Subtotal, individual.....	3	91	6	133	6	133
Institutional awards:						
Noncompeting.....	70	2,402	69	2,360	69	2,360
Competing:						
Renewal.....	--	--	--	---	--	---
New.....	--	--	--	---	--	---
Subtotal, institutional.....	70	2,402	69	2,360	69	2,360
Total, training.....	73	2,493	75	2,493	75	2,493
Research and development contracts	9	3,937	9	5,215	9	5,105
Facilities construction.....		4,940		---		---
	FTEs		FTEs		FTEs	
Research management and support.....	89	11,597	89	11,433	90	12,559
Total.....		340,898		337,105		319,151
HIV/AIDS.....	(7)	(45,274)	(8)	(46,096)	(8)	(48,379)

NATIONAL INSTITUTES OF HEALTH

Research Resources

CROSSWALK - 1989 Actual
(Dollars in thousands)

PROGRAM ACTIVITY	MECHANISM								
	Research Grants			Training Programs		Research and Development Contracts	Research Management and Support	Extramural Facilities	Total
	Research Projects	Research Centers	Other Research	Indiv.	Instit.				
Clinical research....		$107,474	$956			$300			$108,730
Biomedical research technology.....		34,845	4,764			1,334			40,943
Laboratory animal sciences and primate research.....		47,996	16,176	$91	$2,402	222			66,887
Biomedical research support.....			88,762						88,762
Biological models and materials research..		615	1,031			2,081			3,727
Research centers in minority institutions		15,312							15,312
Research facilities improvement.....								$4,940	4,940
Research management and support.....							$11,597		11,597
Total.....		206,242	111,689	91	2,402	3,937	11,597	4,940	340,898

NATIONAL INSTITUTES OF HEALTH

Research Resources

CROSSWALK - 1990 Appropriation
(Dollars in thousands)

PROGRAM ACTIVITY	MECHANISM								
	Research Grants			Training Programs		Research and Development Contracts	Research Management and Support	Extramural Facilities	Total
	Research Projects	Research Centers	Other Research	Indiv.	Instit.				
Clinical research....		$115,284	$617			$163			$116,064
Biomedical research technology.....		32,074	5,605			2,403			40,082
Laboratory animal sciences and primate research.....		49,091	15,574	$133	$2,360	713			67,871
Biomedical research support.....			78,788						78,788
Biological models and materials research..	$749	1,342	1,337			1,936			5,364
Research centers in minority institutions		17,503							17,503
Research facilities improvement.....								---	---
Research management and support.....							$11,433	---	11,433
Total.....	749	215,294	101,921	133	2,360	5,215	11,433	---	337,105

NATIONAL INSTITUTES OF HEALTH

Research Resources

CROSSWALK - 1991 Estimate
(Dollars in thousands)

PROGRAM ACTIVITY	MECHANISM							
	Research Grants			Training Programs		Research and Development Contracts	Research Management and Support	Total
	Research Grants	Research Centers	Other Research	Indiv.	Instit.			
Clinical research....		$116,082	$617			$158		$116,857
Biomedical research technology.....		32,087	5,605			2,325		40,017
Laboratory animal sciences and primate research.....		49,701	15,631	$133	$2,360	738		68,563
Biomedical research support.....			52,966					52,966
Biological models and materials research..	$787	1,342	1,343			1,884		5,356
Research centers in minority institutions		22,833						22,833
Research facilities improvement.....								---
Research management and support.....							$12,559	12,559
Total.....	787	222,045	76,162	133	2,360	5,105	12,559	319,151

NATIONAL INSTITUTES OF HEALTH

Research Resources

Summary of Changes

1990 Estimated budget authority	$337,105,000
1991 Estimated budget authority	319,151,000
Net change	-17,954,000

	1990 Current Estimate Base		Change from Base	
	Pos. (FTE)	Budget Authority	Pos. (FTE)	Budget Authority
Changes:				
A. Built-in:				
1. Within grade increases	---	$4,307,000	---	+55,000
2. Annualization of January 1990 pay raise	---	4,307,000	---	+44,000
3. One extra day of pay	---	4,307,000	---	+21,000
4. Federal Employees Compensation Fund	---	22,000	---	+2,000
5. FTS rate increase	---	88,000	---	+2,000
6. Payment for centrally furnished services	---	2,628,000	---	+514,000
7. Service and supply fund	---	1,098,000	---	+52,000
8. Increased costs of laboratory materials and other supplies	---	3,400,000	---	+91,000
9. DHHS Working Capital Fund	---	185,000	---	-9,000
10. 1991 cost of January 1991 pay raise	---	4,307,000	---	+252,000
Subtotal	---		---	+1,024,000
B. Program:	No.	Amount	No.	Amount
1. Research project grants:				
a. Noncompeting	---	---	+4	+787,000
a. Competing	4	749,000	-4	-749,000
Total	4	749,000	---	+38,000
2. Research centers	207	215,294,000	+3	+6,751,000
3. Other research	928	101,921,000	+20	-25,759,000
4. Research and development contracts	9	5,215,000		-110,000

Summary of Changes - Continued

	1990 Current Estimate Base		Change from Base	
	Pos. (FTE)	Budget Authority	Pos. (FTE)	Budget Authority
B. Program:				
5. Research management and support.....	89	11,433,000	+1	+102,000
Subtotal.....				-18,978,000
Total changes.....				-17,954,000

NATIONAL INSTITUTES OF HEALTH

Research Resources

Budget Authority by Activity
(Dollars in thousands)

	1989 Actual		1990 Appropriation		1991 Estimate	
	FTEs	Amount	FTEs	Amount	FTEs	Amount
Clinical research	--	$108,730	--	$116,064	--	$116,857
Biomedical research technology	--	40,943	--	40,082	--	40,017
Laboratory animal sciences and primate research	--	66,887	--	67,871	--	68,563
Biomedical research support	--	88,762	--	78,788	--	52,966
Biological models and materials research	--	3,727	--	5,364	--	5,356
Research centers in minority institutions	--	15,312	--	17,503	--	22,833
Research facilities improvement	--	4,940	--	---	--	---
Research management and support	89	11,597	89	11,433	90	12,559
Total, budget authority	89	340,898	89	337,105	90	319,151
HIV/AIDS	(7)	(45,274)	(8)	(46,096)	(8)	(48,379)

NATIONAL INSTITUTES OF HEALTH

Research Resources

Budget Authority by Object

	1990 Appropriation	1991 Estimate	Increase or Decrease
Total number of full-time permanent positions	89	90	+1
Total compensable work years:			
Full-time equivalent employment	91	92	+1
Full-time equivalent of overtime and holiday hours	2	2	--
Average ES salary	$73,400	$73,400	--
Average GM/GS grade	9.9	9.9	--
Average GM/GS salary	$36,929	$36,929	--
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	65,806	65,806	--
Personnel compensation:			
Full-time permanent	$3,316,000	$3,672,000	+356,000
Other than full-time permanent	195,000	204,000	+ 9,000
Other personnel compensation	140,000	143,000	+ 3,000
Total, personnel compensation	3,651,000	4,019,000	+368,000
Personnel benefits	646,000	698,000	+ 52,000
Benefits for former personnel	10,000	10,000	---
Travel and transportation of persons	228,000	236,000	+ 8,000
Transportation of things	34,000	35,000	+ 1,000

	1990 Appropriation	1991 Estimate	Increase or Decrease
Rent, communications, and utilities....	237,000	245,000	+ 8,000
Printing and reproduction.....	219,000	225,000	+ 6,000
Other services:			
Project contracts.....	5,215,000	5,105,000	-110,000
Centrally furnished services.....	2,628,000	3,142,000	+514,000
Other.....	3,530,000	3,689,000	+159,000
Supplies and materials.....	117,000	120,000	+ 3,000
Equipment.....	133,000	140,000	+ 7,000
Grants, subsidies & contributions.....	320,457,000	301,487,000	-18,970,000
Total, budget authority by object....	337,105,000	319,151,000	-17,954,000

NATIONAL INSTITUTES OF HEALTH

Research Resources

Significant Items in House and Senate Appropriations Committee Report

Item	Action taken or to be taken
1990 House Report	
1. "The Biological Models and Materials Resources (BMMR) section ... supports research and resources to provide non-mammalian organisms to the biomedical research community. The Committee is fully supportive of this effort and has added sufficient funds to double research in this area." (page 83)	The FY 1990 appropriation for the DRR includes $5,364,000 for the Biological Models and Materials Research Program, a 44 percent increase over the FY 1989 level of $3,727,000.
2. "The Committee will partially restore funding for the regular biomedical research grants (BRSG's) to a level of $44.4 million which is $10 million less than last year. While the Committee is supportive of this program, current budget limits have made it impossible to fully restore it to the 1989 level. The Committee also notes that funding for this program has been a low priority for Director of NIH." (page 83)	The FY 1990 appropriation for the the DRR includes $44,385,000 for the Biomedical Research Support Grant program, a decrease of of $10,788,000 from the FY 1989 level of $55,173,000. The budget request for FY 1991 includes $17,700,000 for the BRSG program to carry out a revised program to increase the participation of women, minorities and disadvantaged persons in biomedical research.
3. "The Committee has been particularly impressed with the Minority High School Apprenticeship program and has included a small increase for this program." (page 83)	The FY 1990 appropriation for the DRR includes $1,810,000 for the Minority High School Student Research Apprentice program, an increase of $136,000 over the FY 1989 level. This increase will allow the support of approximately 1,207 apprentices.
1990 Senate Report	
1. "The Committee recognizes the growing dependence of the biomedical research community on the scientific resources provided by the primate centers. The Committee is concerned about the erosion of the base grant support	The FY 1990 appropriation for the DRR includes $37,129,000 for the support of the Primate Research Centers, an increase of $686,000 over the FY 1989 level.

Item	Action taken or to be taken
for the centers.... The Committee, therefore, urges the Director to review the funding needs of the primate centers and make every effort to shore up their core grant support in fiscal year 1990." (page 156)	
2. ". . .the Committee is greatly concerned with the recent decision by the DRR's National Advisory Council to discontinue support of the only GCRC located in a school of dental medicine. . . . The Committee believes that this decision establishes an unfortunate and unsupportable precedent that will exclude general oral health research and research carried out in schools of dental medicine from future GCRC support. The Committee is further concerned with the arbitrary nature of this decision, as there has not previously been an issue as to whether this oral health GCRC Program falls within the scope of the overall effort at DRR. . . .the Committee believes that the DRR should make appropriate arrangements to ensure that all areas of research interest, including oral health research conducted by schools of dental medicine, can be accommodated within the GCRC Program." (page 156-157)	Through the General Clinical Research Centers Program, the Division of Research Resources provides the clinical research infrastructure to host all areas of research interests, including oral health research. All existing GCRCs are available to host oral health research and many do. Decisions to support GCRCs are based on scientific merit, determined through the peer review process.
3. "The Committee strongly supports the biological models and materials research activity which continues its support of the exploration and development of alternatives to the use of mammalian animals in biomedical research and urges that additional funding be provided to this activity. The Committee strongly supports the development and utilization of alternative research models which do not rely on the use of animals and recognizes the newly created National Coalition for Scientific Alternative Resources [NCSAR], a growing coalition comprised of numerous organizations representing existing	The Division of Research Resources established the Biological Models and Materials Research (BMMR) Program in October 1989 to provide for the development and support of nonmammalian models for biomedical research, and to provide support for biological materials resources. Increased funding has enabled the BMMR program to issue a request for applications in December 1989 to solicit Research Project Grant (RPG) applications on alternative research models. The BMMR program is planning to fund four to six meritorious applications this year. The FY 1990 appropriation for the DRR includes

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Item	Action taken or to be taken
and emerging biomedical and biotechnological alternative resource development. One of NCSAR's founding members is the National Disease Research Interchange [NDRI], whose mission is to ensure regular access to human tissues and organs for biomedical researchers throughout the country. Breakthroughs in the treatment and cure of many diseases can be expected through the development of these alternative resources." (page 157)	$5,364,000 for the BMMR Program, a 44 percent increase over the FY 1989 level of $3,727,000.
4. "Consistent with the congressional mandate directing NIH to develop research methods which do not rely on the use of animals, the Committee urges the Division of Research Resources to consider establishing a division of alternative resources program that is separate and distinct from the Animal Resources Program, and to give this effort priority and visibility in fiscal year 1990." (page 158)	In October of 1989, the DRR established the Biological Models and Materials Research Program Branch, thus separating this program from the Animal Resources program, and giving the effort enhanced visibility and a higher priority.
5. "The Committee urges the Division of Research Resources to continue its support of nursing research through the General Clinical Research Centers Program and the Biomedical Research Support Program." (page 158)	Through the General Clinical Research Centers and the Biomedical Research Support Program, the Division of Research Resources continues to support nursing research. The national network of GCRCs hosts over 200 nurses who participate in more than 200 nursing research projects at 50 to 55 centers. Many of these projects concern AIDS Research. In fiscal year 1989, the Biomedical Research Support Grant (BRSG) Program awarded appropriately $350,000 in support to 20 Schools of Nursing affiliated with Universities across the nation, an increase of 22 percent over 1988.

NATIONAL INSTITUTES OF HEALTH

Research Resources

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1990 Amount Authorized	1990 Appropriation	1991 Amount Authorized	1991 Budget Estimate
Research and Investigation.....	Section 301	42§241	Indefinite		Indefinite	
Division of Research Resources..	Section 479,480	42§287 287a,300a, and 5§332	Indefinite	$334,612,000	Indefinite	$316,658,000
National Research Service Awards	Section 487	42§288	Such sums as necessary 1/	2,493,000	Authorizing Legislation to be requested	2,493,000
Total Budget Authority.....				337,105,000		319,151,000

1/ This training authority is shared with other research training programs of the National Institutes of Health and the Alcohol, Drug Abuse, and Mental Health Administration.

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NATIONAL INSTITUTES OF HEALTH

Research Resources

Appropriations History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1982	$168,839,000 2/	$191,965,000	$191,967,000	$184,177,000
1983	191,024,000	227,642,000	199,967,000	213,912,000
1984	201,832,000	253,824,000 3/	230,031,000 3/	244,977,000 4/
1985	247,528,000	305,331,000 5/	305,298,000	304,025,000
1986	263,040,000	304,579,000 6/	305,739,000	305,667,000
1986 Sequester				-13,144,000
1987 7/	234,192,000	317,826,000	319,924,000	322,860,000
1988	280,415,000	346,652,000 8/	367,415,000	368,153,000
1989	319,977,000 9/	355,767,000 10/	367,987,000	358,608,000 11/ 13/
1990	263,313,000 12/	356,128,000	362,253,000	353,734,000
1991	319,151,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.
2/ Reflects the September amendment; the original request was $191,863,000.
3/ Excludes $720,000 in NRSA training programs not considered.
4/ Includes $708,000 for NRSA training programs authorized under a Continuing Resolution.
5/ Excludes $775,000 in NRSA training programs not considered.
6/ Excludes $1,029,000 in NRSA training programs not considered.
7/ The budget estimate to Congress proposed that all funding for AIDS research be consolidated in the Office of the Assistant Secretary for Health. The House allowance consolidated all NIH AIDS funding in the Office of the Director, NIH; the Senate allowance and the appropriation spread funding among the institutes, including $6,142,000 for the Division of Research Resources.
8/ Does not include funding for AIDS research which was consolidated at the Secretary's level.
9/ The 1989 request excludes funds for AIDS research and education ($38,010,000) proposed for consolidation in the Office of the Assistant Secretary for Health.
10/ Excludes $2,220,000 in NRSA training programs not considered.

11/ Reflects a 1.2% reduction ($4,356,000) and a reduction of $23,000 as a result of improved procurement practices from the appropriated level of $362,987,000 as required by P.L. 100-436 Sections 517 and 215 respectively.

12/ The 1990 request excludes funds for the National HIV program ($44,643,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

13/ Reflects reductions of $16,000 for procurement savings; $344,000 for extramural salary cap and $97,000 for salaries and expenses.

Justification

Research Resources

	1990 Appropriation		1991 Estimate		Increase or Decrease	
	FTEs	BA	FTEs	BA	FTEs	BA
TOTAL...	89	$337,105,000	90	$319,151,000	+1	-$17,954,000
HIV/AIDS	(8)	(46,096,000)	(8)	(48,379,000)	(--)	(+2,283,000)

General Statement

The Division of Research Resources (DRR) is responsible for the development, support and administration of the resources which are essential in order to maintain the quality of the research infrastructure in which investigators conduct state-of-the-art biomedical research. The Division carries out this responsibility by awarding research grants, contracts, cooperative agreements, facility improvement grants, and training grants to fill a wide variety of institutional research resource needs, and by providing technical expertise, information exchange and research opportunities to investigators.

Today's science depends upon investigators having access to sophisticated instrumentation, well-equipped laboratories, and laboratory animals; the availability of biological models and materials critically needed for the study of human disease; dissemination of information about new technologies and the equipment necessary to employ new research techniques; the availability of clinical research environments so that laboratory advances can be rapidly translated to human health care; and large capacity computers for the analysis of data. Researchers may require high field nuclear magnetic resonance spectrometers to study biomacromolecules, computers to analyze and model the physiology of disease and its treatment, microsensors to monitor patients noninvasively, or access to a synchrotron beam radiation resource for the study of viruses, including AIDS. Clinical investigators need specialized clinical environments where they can apply laboratory research advances such as computerized axial tomography and recombinant DNA-produced compounds to the treatment of human health problems, or where they can conduct clinical trials of new drugs and therapies. Laboratory animals may be used for multiple studies including testing the safety and effectiveness of diagnostic and treatment techniques prior to clinical trials in humans.

Through its six extramural programs the Division provides support to develop and ensure the availability of such resources. The Clinical Research Program supports the development and maintenance of specialized clinical research environments within large hospitals. The Biomedical Research Technology Program provides biomedical researchers access to the latest

technologies from the physical sciences, mathematics, and engineering. The Laboratory Animal Sciences and Primate Research (LASPR) Program supports projects that focus on the most effective use of animals in research and the development of appropriate animal models; support is provided as well for the Regional Primate Research Centers and a number of unusually valuable research animal colonies, and for essential animal facility improvement awards. The LASPR Program also supports the only NIH extramural research training program which provides postdoctoral research training in laboratory animal science for veterinarians. The Biological Models and Materials Research (BMMR) Program is developing the uses of cell systems, lower organisms and nonbiological systems as models in biomedical research. The Biomedical Research Support (BRS) Program enables institutions to conduct research programs more effectively and efficiently, using local decision-making to determine how best to use the BRS formula grant funds (for equipment and facilities, pilot research projects,support of new investigators, and/or for emergency research needs.) A major refocussing of the formula program is planned for FY 1991; one third of the funds requested will be directed to institutions which have increased the participation of underrepresented minorities and disadvantage persons in biomedical research; this proposal is discussed in greater detail in the BRS section of the Justification. Also within the Biomedical Research Support Program, the BRS-Shared Instrumentation Grant Program provides funds for the purchase of up-to-date research instruments to be shared by groups of PHS-grant supported biomedical researchers. The BRS Program also provides the support for the Minority High School Student Research Apprentice Program, a highly successful method for introducing minority students to the field of health research.

The Research Centers in Minority Institutions Program supports the development and enhancement of the research infrastructure of predominantly minority institutions, to make these institutions more competitive in seeking NIH and PHS research project grant support. In the past this program has been funded in the Office of the Director, NIH; this year, however, it is proposed for appropriation to the DRR which has administered the program since its inception.

The Minority Biomedical Research Support Program, supporting both the participation by ethnic minority students and faculty in research in the biomedical and behavioral sciences and the development of the research and research training capabilities of the institutions that serve minority populations, has been transferred to the National Institute of General Medical Sciences in FY 1991.

The Research Facilities Improvement Program, a program providing for the repair, renovation, modernization, and expansion of existing facilities for the conduct of AIDS research, has awarded all the funds provided by Congress in FY 1988 and FY 1989, and no further funds are requested in this budget.

Overall Budget Policy

The FY 1991 budget request for the Division of Research Resources is $319,151,000. This level of support will enable the Division to continue its ongoing activities in FY 1991. Most DRR programs and mechanisms will be

funded at approximately the same level as the comparable FY 1990, with the exception of the Biomedical Research Support Grant Program, which has been proposed for a major change in the mission of the program, focussing resources on the development and encouragement of minority investigators at recipient institutions. Also in response to the Secretary's emphasis on programs benefitting minorities, the Minority High School Student Research Apprentice Program is proposed for an increase of 46 percent, and the Research Centers in Minority Institutions for a 30 percent increase. AIDS and AIDS-related research is proposed for a modest increase in FY 1991.

In 1991, the DRR will support 4 noncompeting research project grants, the continuation costs of the grants funded by DRR for the first time in 1990 in the Biological Models and Materials Research (BMMR) Program. This small research project grant program was part of a substantial increase provided to the BMMR Program by Congress in 1990.

In FY 1991, the Division will support 210 research centers, most at approximately the same level of support as in FY 1990. The Division will maintain support to 78 general clinical research centers; 59 biomedical research technology centers; 7 primate research centers; 40 laboratory animal science centers; and 6 biological models and materials research centers. As indicated above, the 20 research centers in minority institutions will receive a substantial increase in support over FY 1990.

The FY 1991 request includes $3.0 million to continue to address the repair and renovation needs of the Primate Research Centers: to improve sewage disposal systems; renovate ventilation and sanitation equipment; provide additional caging and cage washing equipment; and replace obsolete central research equipment.

The Animal Facilities Improvement Program will be continued in FY 1991 at a funding level of $10.9 million. It is expected that this level will support approximately 37 awards.

The Division recognizes the importance of stabilizing its support for research instrumentation, and the request provides $32.6 million in the Shared Instrumentation Grant Program. This will support approximately 137 shared instrumentation grants.

The Minority High School Student Research Apprentice Program is proposed for an increase of 46 percent in FY 1991. This will enable the Division to support approximately 1,764 high school students in summer training programs designed to introduce them to health-related research, and attract them into careers in the health field.

The FY 1991 request for research training is $2,493,000, the same level as in both FY 1989 and FY 1990. This level will enable the Division to support approximately 69 institutional trainees and 6 individual fellowships in FY 1991.

The budget request for research and development contracts is $5,215,000. This level will allow for the support of nine contracts in FY 1991.

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The FY 1991 budget request for Research Management and Support is $12,559,000. This level reflects an increase of $1,024,000 for built-in administrative cost increases, and $102,000 in program increases over the comparable FY 1990 level.

Research Resources

Management Savings

As a result of final Congressional action on the FY 1990 appropriations bill, the Division of Research Resources reflects a reduction of $250,000 in the research management and support activity in response to the Senate Committee's directive to reflect savings related to the merger of the Division of Research Resources and the Division of Research Services. These savings will be achieved through reductions in selected overhead positions and actions taken to streamline administrative functions. It is expected, however, that most of the administrative savings and reductions in FTEs resulting from this reorganization will be long term so as to avoid immediate personnel dislocations.

Program Accomplishments

The Division's programs have been integrally involved in a number of scientific accomplishments over the past year that relate to a wide range of diseases and disorders. Some examples follow.

Investigators supported by BRSG funds have developed a novel new antimalarial drug--tetrandrine, an alkaloid isolated from an ancient Chinese medicinal plant. The antimalarial activity was tested in vitro, using human cells that were infected with Plasmodium falciparum, the disease-causing parasite. The investigators found that tetrandrine was three times more toxic to chloroquine-resistant strains than to sensitive strains of Plasmodium. This suggests that a combination of chloroquine and tetrandrine may prevent the emergence of chloroquine resistance. The drug appears to have a low toxicity in animals and humans.

Cardiovascular surgeons at the University of Washington Regional Primate Research Center have taken another step toward the development of artificial blood vessels to bypass or replace segments of arteries blocked by atherosclerosis. The blocked artery can be replaced by a blood vessel from another part of the body or by an artificial vessel. Up to now, neither has been a perfect substitute. Currently available materials used for artificial bypass grafts can fail by causing a blood clot to form that blocks the vessel again or breaks off and travels in the blood stream to cause problems in another part of the body.

The most recent advance in this area has been the discovery that more porous graft materials than those currently used allow the rapid ingrowth of tiny blood vessels (capillaries) through the wall of the artificial vessel. These capillaries provide a source of the body's own cells that grow to cover the inner surface of the artificial vessel. The new lining develops within about two weeks. The cells forming the lining are the same as those that line normal arteries, thus they produce substances that prevent clotting and should prevent failure of the graft. As a direct result of this work, grafts made of the new porous material are now being tested in patients with arterial blockage caused by atherosclerosis.

A new and safe treatment to restore bone loss occurring in spinal osteoporosis has been proven in clinical tests at the University of Texas Southwestern Medical Center GCRC in Dallas. The treatment combines a new slow-release form of sodium fluoride with a calcium citrate supplement -- a combination that increases bone mass and remineralizes bone. This treatment is intended to help patients who have already sustained substantial bone loss and decrease their risk of developing fractures of the spine. To date, more than 300 patients have been monitored during treatment for an average of 3.5 years. Following treatment, bone density in the lumbar spine increased or at least stabilized. Patients showed average annual increase of 5.1 percent in bone mass for up to 4 years of study. Bone biopsy documented an increased amount of normally mineralized bone, which was mechanically intact or improved. Adverse complications were minor.

Historically, the analysis of human-pedigree data has been most successful in identifying single genes that cause very rare diseases, each with a prevalence of less than one in a thousand. The commoner diseases,

with lifetime prevalence of 1 percent or more, appear to be due to a complex interaction of many environmental and genetic factors. Although single genes are involved, the genetic component has usually been termed "polygenic" for want of a more detailed analysis. But each single gene affects many different phenotypic traits and, by analyzing these jointly on pedigree data, it should be possible to identify the action of single genes.

Investigators at the Louisiana State University Medical Center have devised a statistical method of doing just this, making use of the fact that all genes, when transmitted from one generation to the next, tend to congregate with other genes that are located close by on the chromosomes. Using this method, they believe they have identified the chromosomal location of a common gene that predisposes to heart attacks. This new method of analysis will become increasingly important for the genetic study of common diseases as the human genome initiative progresses.

Lyme Disease, a disorder caused by the spirochete, Borrelia burgdorferi, produces a variety of symptoms, including chronic inflammation of joint membranes. Although antibiotics are usually effective early in the course of the disease, longer courses of therapy are often needed as the illness progresses--and some patients do not respond at all. Studies supported by BRSG funds may have profound implications for the clinical course of this disease, as well as development of new therapies. Investigators have shown that the bacterium can penetrate the membrane of cultured endothelial cells, pass into the cytoplasm, and then exit the cells. Thus, the spirochete could use the cell as a shelter from the body's immune response. The findings may explain why patients with Lyme Disease experience asymptomatic periods. Further, these results suggest that a therapy capable of blocking the initial interaction of the spirochete within the host cell may prevent the disease from progressing. These studies are continuing with a grant from the National Institute of Allergy and Infectious Diseases.

Researchers at the Brigham and Women's Hospital GCRC in Boston, Massachusetts, continue to study converting enzyme inhibitors (CEIs), a new class of drugs for the treatment of high blood pressure. CEIs effectively lower blood pressure in all forms of hypertension, whether mild, moderate, or severe. They are equally effective in patients of both sexes and all ages. The inhibitors are as effective as diuretics in the hypertensive elderly, but they are less effective in black patients than in non-black patients and less effective than diuretics in blacks. However, when combined with diuretics, they are equally effective in blacks and non-blacks, and the combination is more effective than either drug alone.

Investigators in a DRR-supported Autoradiographic Image Processing Center have developed a computer program that is widely used in analyzing brain images to track changes in the chemistry of the brain occurring during degenerative disorders such as Parkinson's disease and Alzheimer's disease. Numerous research projects on nondegenerative disorders also use this image analysis system; these include studies on the neurochemistry of epilepsy at Yale University, the neurochemistry of ischemia at the University of Utah, and the basis for drug addiction at the University of Virginia Medical School.

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Scientists at the Harvard Medical School--McLean Hospital have used BRSG funds to conduct a pilot study which showed that the drug buphrenophine, a pain reliever, suppresses the self-administration of cocaine by rhesus monkeys. The drug did not have a blanket suppressing effect on behavior but altered specifically the drive for cocaine. Clinical studies are now underway to determine whether the analgesic will help humans overcome dependence on cocaine and heroin.

AIDS Research Program

DRR AIDS Research Program

AIDS research and the provision of resources for AIDS research have become an important focus within the Division of Research Resources. The growth of the NIH-supported AIDS research programs in recent years has created increased demands for research space; for upgraded laboratory, clinical, and animal facilities; and for the scientific equipment necessary to conduct AIDS research safely and efficiently.

Recent Research Accomplishments

The general clinical research centers (GCRCs) are a major network supporting a wide array of AIDS-related clinical research studies. The number of AIDS-related research projects and the number of GCRC sites hosting HIV-related research has increased dramatically in the past few years. The rate at which AIDS research protocols have been introduced at those sites is unprecedented for a single area of research in the history of the program. GCRCs undergird many of the studies conducted by the AIDS Clinical Trial Units, the Multicenter AIDS Cohort study, and the National Cooperative Drug Discovery Program for the treatment of AIDS. Additionally, many cooperative agreements and investigator-initiated AIDS research protocols are also supported through the GCRC network. The number of AIDS patients enrolled in the foregoing studies has continued to increase.

A study was conducted at the Baylor College of Medicine Pediatric General Clinical Research Center to define opportunistic infections (OI) that were most prevalent and linked with the highest mortality rate in that urban pediatric population. Seventy-three pediatric HIV patients followed up to 7 years were reviewed for evidence of OI. As in the adult population, Pneumocystis carinii pneumonia (PCP) was the most frequently reported opportunistic organism with a high mortality rate linked to both clinical presentation with acute respiratory failure and co-infection with cytomegalovirus (CMV). CMV infection had the highest mortality rate with documented pneumonitis, hepatitis and retinitis. The incidence of OI was 25% with mortality high for PCP, CMV, and gram negative sepsis.

The simian immunodeficiency viruses (SIVs), first discovered at the New England Regional Primate Research Center are nonhuman primate lentiviruses that are the closest known relatives of HIV-1 and HIV-2, the viruses that cause AIDS in humans. The most important feature of the SIVs is their capacity to be used in animals to model AIDS. Their usefulness stems from: 1) the extensive similarities of SIV to HIV in genetic makeup and biological properties; 2) the capacity to induce AIDS in rhesus monkeys in a time frame suitable for laboratory investigation; and 3) the availability of rhesus monkeys as experimental animals. Studies in SIV systems have already resulted in several contributions regarding the origins of the HIVs, AIDS pathogenesis and vaccine and drug therapy research.

The Primate Research Centers are continuing their activities in AIDS research. Recently, investigators at the Delta Regional Primate Research

Center found that immunization with a killed whole SIV vaccine prevented infection and disease in eight to nine rhesus monkeys (90%) experimentally exposed to infectious virus. Immunization with a viral envelope-enriched subunit vaccine has prevented infection and disease in two of four monkeys (50%) experimentally exposed to infectious virus. All non-immunized control monkeys (five of five monkeys or 100%) exposed to the same virus preparation became infected and have AIDS; three have died. The success of these studies suggests that a vaccine for an AIDS virus can induce a high degree of protection from both infection and disease.

The National Chimpanzee Breeding and Research (NCBR) Program was initiated in September 1986. The objective of the program is to ensure the survival of the chimpanzee and its availability to researchers by creating colonies of behaviorally normal noncontagious chimpanzees to be used primarily for breeding. Since the chimpanzee is the only animal species in which HIV has been found to survive, anticipated expansion in the use of chimpanzees for the development and evaluation of candidate AIDS vaccines is expected. The chimpanzees produced in the breeding and research program will not initially be involved in these studies. These chimpanzees are intended to replace those animals that are currently available. As variations on the type of vaccine become available, additional uninfected chimpanzees will be required for testing. The NCBR Program has been remarkably successful: over 100 births have occurred in the program so far, and the research carried out has been successful in identifying ways of resocializing orphan-raised animals, improving infant survival, and enriching the environment of captive chimpanzees.

The large increases in the NIH-supported AIDS research programs have created needs for additional research space; upgraded clinical, laboratory, and animal facilities; and related equipment necessary for the safe and efficient conduct of AIDS research. In order to meet these needs, the Congress provided $23,935,000 in 1988 and $4,940,000 in 1989 for a new program -- the Research Facilities Improvement (RFI) Program. These funds were obligated in 1989 for 50 projects to provide for the repair, renovation, modernization, and expansion of existing facilities that are being used for the conduct of AIDS or AIDS-related research, and for the purchase of associated equipment.

At the Public Health Research Institute in New York City, BRSG funds were used to support pilot studies on the development of an ultra-high sensitivity assay for the detection of pathogenic retroviruses such as HIV-1. In general, the sensitivity of nucleic acid hybridization assays is limited by the ability to detect probes once they have found their targets. The practical limit of current clinical assays is one million molecules, but infectious agents often cause disease at titers below this level of detection. This method utilizes recombinant RNAs that contain an embedded hybridization probe sequence. Thus, these recombinants are bifunctional, having both a specific gene probe and the ability to be amplified by Q Beta replicase. After the probe portion of the recombinant molecule has been bound, and unbound probes are washed away, replicase is added and the amplified signal of the presence of target organisms is generated. One billion copies of the RNA molecule can be made in 30 minutes. Amplification

of the replication of the RNA molecules as a basis for the development of extremely sensitive clinical assays is now being explored under a grant from NHLBI.

X-ray diffraction structural measurements have greatly extended our knowledge and understanding of proteins, the molecules which perform many of life's functions. These methods have now been extended to the much larger structure of viruses, which cause many diseases including AIDS. Because of the large size of viruses and their sensitivity to x-rays, these structures usually must be obtained using diffraction data from the very intense radiation beams of synchrotron sources. Recently researchers at synchrotrons have determined structures of plant and bacterial viruses, and even human viruses such as the rhinovirus which causes colds. Now the Biomedical Research Technology Program of DRR is providing funds for the construction of an x-ray structural analysis beam line that will meet advanced biological-containment requirements so that it may be used for the determination of structures of highly virulent agents such as components of HIV. Two other NIH components, NIAID and NIGMS, contributed funds toward the renovation costs. This will be the only facility in the world equipped for experiments with pathogenic materials using synchrotron radiation.

Researchers at the Morehouse School of Medicine in Atlanta, Georgia, who receive support through the Research Centers in Minority Institutions (RCMI) Program, have established immortalized cultures of human retinal pigment epithelial cells on collagen gels using protooncogenes and have determined that the human immunodeficiency virus (HIV) replicates in these cells after transfection. The system will be used by scientists as a model to investigate HIV infection of ocular tissues and to determine how HIV modulates the expression in these tissues of cytomegalovirus, a major cause of blindness in AIDS patients.

Research Plans

The 1991 budget request for AIDS and AIDS-related research is $48,375,000, an increase of five percent over the comparable 1990 level of $46,096,000. This increase will permit the DRR to continue support for all of its programs in AIDS research, from providing infrastructure and research support for clinical trials to the development and utilization of animal models for vaccine research. Research on human immuno-deficiency virus and AIDS, including HIV in minority populations, will continue to be conducted by all the DRR programs at a slightly increased level from 1990.

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Research Resources

Clinical Research

Authorization: Indefinite.

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$116,064,000	$116,857,000	+$793,000

Purpose and Method of Operation

The General Clinical Research Centers (GCRC) provide the clinical research infrastructure to investigators who receive their primary research funding predominantly from the categoric research institutes at the National Institutes of Health. Consequently, through its clinical research facilities, specialized personnel and sophisticated laboratories, the national network of GCRCs host an array of research which reflects the research missions of the several disease-oriented institutes of the National Institutes of Health. More than 7,000 investigators use one or more resources at GCRCs to study the pathophysiology and examine therapeutic approaches to a wide array of disorders that affect children and adults.

Since inception of the Clinical Associate Physician Program in the mid-1970s, 189 physician-investigators have graduated from that Program. Each year approximately 15 new applicants are funded for up to three years through this GCRC career development program. The development of highly qualified clinical investigators assures that basic research advances will continue to be incorporated into understanding and treating clinical disorders and ultimately be translated into standard medical practice.

The GCRCs constitute a major resource for the study of rare diseases as well as for many other disorders such as hypertension, diabetes, and acquired immune deficiency syndrome (AIDS). The GCRCs play an integral role in hosting the clinical research studies of the Pediatric and Adult AIDS Clinical Trials Groups as well as many other investigator-initiated studies of AIDS. Relative to FY '88, there was a 40 percent increase in the number of AIDS-related research projects hosted by 52 of the 78 GCRCs in FY '89. The scope and complexity of AIDS-related research will continue to increase across the centers.

Studies at a number of centers, including the Adult GCRC at the University of California, San Francisco, tested aerosolized pentamidine therapy for mild to moderate *Pneumocystis carinii* pneumonia. The satisfactory response rate was approximately 80% with no major side effects. The early relapse rate, reflected by recurrence of disease within three months of completion of therapy, was high (67%). Relapses occurred

despite administration of pentamidine prophylaxis within one month of the completion of therapy. This study showed that Pneumocystis carinii pneumonia can be managed with aerosolized pentamidine, which is effective and nontoxic, but associated with a high rate of early relapses.

Scientists at the University of California, San Francisco, Pediatric GCRC have continued a prospective evaluation of infants at risk for human immunodeficiency virus (HIV) infection born to intravenous-drug-using women. An early sign of HIV infection in infants is an abnormally high level of circulating antibody. Efforts continue to discriminate infected from uninfected infants born to HIV-infected mothers by either measuring IgG antibody levels (valid only after age 15 months) or viral cultures which have low sensitivity and are costly. The usefulness of amplification of HIV in white blood cells by polymerase chain reaction (PCR) was evaluated in infants at high risk of HIV infection. PCR and concurrent viral cultures were compared, using peripheral blood mononuclear cells from high-risk subjects. Simultaneously performed HIV cultures concurred with PCR results for all infected patients. This study demonstrates that PCR can be used for the rapid, early and definitive detection of HIV infection in infants at high risk.

Investigators at the Johns Hopkins GCRC in Baltimore, Maryland, examined patients with early probable Alzheimer's disease and age-matched healthy subjects. The patients were scanned with an x-ray technique - computerized axial tomography - at yearly intervals; the normal subjects were rescanned after four years. Regional volumes of cerebrospinal fluid (CSF) -- the fluid that is secreted by specialized cells into the ventricles which are the fluid-filled compartments of the brain -- were calculated. The GCRC investigators found that CSF volumes were significantly larger after just one year in patients with Alzheimer's disease. The investigators reasoned that the greater the volume of CSF, the larger the ventricles. If no conditions other than Alzheimer's disease are acting on the subjects, ventricles can expand only with the atrophy of brain tissue. Therefore, expanding CSF volumes indicate increasing atrophy or loss of brain tissue. So great was the atrophy, in fact, that the Alzheimer patients showed an increare in CSF volumes after only one year that was significantly greater than the increase seen after four years in the healthy group. Additional studies are planned to determine if this technique may be effective in rapidly identifying early cases of Alzheimer's disease.

The cytokine, interleukin-6, may contribute to the skin abnormalities observed in patients with psoriasis, according to GCRC investigators at Rockefeller University in New York City. Patients with psoriasis have increased blood levels of IL-6 and increased expression of its messenger mRNA in biopsies of affected skin areas. After systemic treatment with antimetabolic or anti-inflammatory agents, patients with psoriasis have significantly lower immunoreactive IL-6 as well as significantly lower IL-6 messenger mRNA in skin biopsied from affected areas. Those observations may provide biochemical endpoints for the development of more effective therapies of patients with psoriasis.

Investigators at the Brigham and Women's Hospital GCRC in Boston, Massachusetts, continue to study converting enzyme inhibitors (CEIs), a new class of drugs for the treatment of high blood pressure. The renin-

angiotensin-aldosterone system, an important hormonal axis, plays a pivotal role in the regulation of volume homeostasis and blood pressure. CEIs act to interrupt this system by decreasing the generation of angiotensin II, a potent vasoconstrictor. CEIs effectively lower blood pressure in all forms of hypertension, whether mild, moderate, or severe. They are equally effective in patients of both sexes and all ages. The inhibitors are as effective as diuretics in the hypertensive elderly, but they are less effective in black patients than in nonblack patients and less effective than diuretics in blacks. However, when combined with diuretics, they are equally effective in blacks and nonblacks, and the combination is more effective than either drug alone.

Investigators at 14 different GCRCs are participating in a multicenter clinical trial to assess whether deprenyl and tocopherol, two antioxidative agents which act through different mechanisms, could slow the progression of symptoms in patients with otherwise untreated Parkinson's disease. Interim analysis of the data revealed that deprenyl significantly delays the onset of disability associated with Parkinson's disease. The study will continue to ascertain the long term therapeutic effects of deprenyl alone or with tocopherol, a component of vitamin E.

Rationale for the Budget Request

The 1991 budget request for the Clinical Research Program is $116,857,000, an increase of $793,000 over the comparable 1990 level. This will enable the Division to support 78 general clinical research centers in 1991, the same number as in 1990.

There will be a continued demand for use of GCRC beds and facilities by research investigators supported by NIH, as a result of research initiatives by the NIH in areas of national concern. The number of clinical trials and research project grants that are using the general clinical research centers continues to increase. The 78 GCRCs will strive to meet this increasing demand and preserve the availability of research beds and the related laboratory resources and skilled personnel for use by biomedical investigators.

Outpatients are entering GCRC studies at a greater rate, to have blood tests and other assays performed in the GCRC core laboratory. They then return home, only to visit the medical center periodically. Outpatient studies are a more cost effective utilization of center resources, but all studies, unfortunately, cannot be carried out in that setting.

The Division will continue to control its overall costs in 1991 by recovering third party insurance payments for hospitalized patients, by conducting more outpatient research studies, and by carefully negotiating the cost of each center. Through these methods, the Division will be able to maintain a strong clinical research resource for the biomedical research community.

Impact Data	1990 Appropriation	1991 Estimate	Increase or Decrease
Research centers			
Number	78	78	---
Amount	$115,284,000	$116,082,000	+$798,000
Other Research			
Number	3	3	---
Amount	617,000	617,000	---
Research & Development Contracts			
Number	1	1	---
Amount	163,000	158,000	-5,000
Total	116,064,000	116,857,000	+793,000

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Research Resources

Biomedical Research Technology Program

Authorization: Indefinite.

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$40,082,000	$40,017,000	- $65,000

Purpose and Method of Operation

Technology is the engine that drives much of biomedical research. The purpose of the Biomedical Research Technology Program is to provide the scientific community access to advanced technologies needed to solve the problems of medical research. This purpose is accomplished by funding centers for the development and application of technologies that are essential to biomedical research, but not widely available. These centers are staffed by gifted scientists and engineers at the forefront of their technological areas who work closely with biomedical scientists from academia, industry, and other laboratories to both develop and apply new technological capabilities to cutting-edge biomedical research problems. In addition to the 59 research centers currently funded the Program funds resource-related research project grants for instrument development, small grants for innovative pilot studies, first independent research support and transition awards, small business innovation research grants, and some contracts.

The distinguishing feature of the Program is its technology focus; the user applications range from molecules to man, as can be seen from some of the recent accomplishments. In the molecular area, a new beam line that can be used for X-ray diffraction studies of crystalline viruses and proteins from pathogenic sources was funded in 1989 at the Cornell High Energy Synchrotron Source. This will be the only synchrotron facility in the world with a biological containment capability to permit the structural studies of crystalline infectious agents such as poliovirus and coat proteins from the AIDS virus and its receptors. A different type of structural research collaboration between a scientist at the University of California, Berkeley, and a mass spectrometry center in San Francisco resulted in the determination of the chemical nature of the signalling mechanism used by bacteria to control the proteins involved in motion. The mechanism involved a transient chemical change that produced a brief biochemical signal. The chemical basis for cellular motility is a major unsolved problem in cell biology. This signalling mechanism could only be studied using novel analysis methods and a very advanced mass spectrometer. The implications for the understanding of the chemical basis of cellular behavior are exciting.

New opportunities in high field nuclear magnetic resonance (NMR) spectroscopy are dependent upon advances in the available instrumentation, in particular the development of high field superconducting magnet technology. At Carnegie Mellon University, the Program is supporting development of a unique NMR magnet which will make available an NMR Spectrometer for biomedical studies at the highest achievable field; the instrument would be the first of its kind and would push the state-of-the-art many years ahead of any commercial instrument available anywhere. These developments in high field nuclear magnetic resonance will provide for new basic research opportunities on biomacromolecules in solution including: detection of fast chemical exchange; molecular orientation and geometric structure; and the dynamics of interaction of biopolymers such as DNA with substrates, drugs, and toxins.

The Program also supports a number of computer analysis and modeling activities related to the physiology of disease and its treatment, and to genetically inherited diseases. Historically, the analysis of human pedigree data has been most successful in identifying single genes that cause very rare diseases, each with a prevalence of less than one in a thousand. The commoner diseases, with lifetime prevalences of 1 percent or more, appear to be due to a complex interaction of many environmental and genetic factors. Each single gene affects many different phenotypic traits, and by analyzing these jointly, on pedigree data, it should be possible to identify the action of single genes. A statistical method of doing just this has been devised at a BRTP center in Louisiana, making use of the fact that all genes, when transmitted from one generation to the next, tend to co-segregate with other genes that are located close by on the chromosomes. An example is the recently proposed linkage between two genes, one that controls diastolic blood pressure and related traits and the other that controls 6-phosphogluconate dehydrogenase (a red blood cell enzyme). If such a linkage can be corroborated using more traditional parametric segregation and linkage analyses, this finding could eventually have a major impact on the treatment for hypertension. This new method of analysis will become increasingly important for the genetic study of common diseases as the human genome initiative progresses.

In the AIDS area, a new center for the analysis of complex carbohydrates was funded in 1989. Investigators at this center recently completed an analysis of the structures of the carbohydrates which coat the primary receptor for the AIDS virus. The carbohydrate coats on cells are the basis for antigenic activity, and the innovative techniques developed at this center should enhance the search for immunologic agents against the AIDS virus.

Rationale for the Budget Request

The 1991 budget request for the Biomedical Research Technology Program is $40,017,000. This level will enable the Division to support 59 resource center grants; 39 resource-related research grants, small grants and conference grants; 13 small business innovative research grants; and 3 research and development contracts.

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The Program will continue to address the instrumentation needs of the biomedical research community by providing advanced instrumentation at biomedical research technology centers, by supporting research on instrument development or new research techniques, and by supporting short-term training in the application of research technologies using high technology instrumentation.

Impact Data	1990 Appropriation	1991 Estimate	Increase or Decrease
Computer resources	$10,034,000	$10,018,000	-$16,000
Biomedical engineering	3,481,000	3,476,000	-5,000
Biological structure and function	26,567,000	26,523,000	-44,000
Total	40,082,000	40,017,000	-65,000
Research centers			
Number	59	59	---
Amount	$32,074,000	$32,087,000	+13,000
Other Research			
Number	52	52	---
Amount	5,605,000	5,605,000	---
Research & Development Contracts			
Number	3	3	---
Amount	2,403,000	2,325,000	-78,000
Total	40,082,000	40,017,000	-65,000

Research Resources

Laboratory Animal Sciences and Primate Research

Authorization: Indefinite.

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$67,871,000	$68,563,000	+$692,000

Purpose and Methods of Operation

The major objective of the Laboratory Animal Sciences and Primate Research (LASPR) Program is to support resource and research activities that enhance the quality and most efficient use of laboratory animals in biomedical research. This is accomplished through research and resource grants, training grants, and cooperative agreements with research institutions to provide specialized resources which are critical to the advancement of scientific progress on many important human health problems, including drug addiction, Alzheimer's disease, Parkinson's disease, cardiovascular diseases, and AIDS. The Program provides support for the resources and biomedical research conducted with nonhuman primates in the seven Regional Primate Research Centers; for comparative medicine research in the diagnostic laboratories; for postdoctoral training of specialists in laboratory animal sciences; for the development of animal models of human diseases; for the improvement of laboratory animal facilities; and for the breeding and supply of special animal resources including chimpanzees, which are vital for research on viral-induced diseases such as AIDS and hepatitis.

The major subdivisions of the LASPR Program are the Regional Primate Research Centers Program and Laboratory Animal Sciences Program. The AIDS Animal Models activities include the Chimpanzee Breeding and Research (CBR) and Specific Pathogen Free Rhesus Breeding and Research (SPFRBR) Programs.

Laboratory Animal Sciences Program

Of the 140 Animal Resource Improvement applications received during FY 1989, 37 projects were funded with a total of approximately $11.1 million. The support was used to renovate laboratory animal facilities, improve the environmental quality of the animal space, upgrade animal caging, and improve sanitation equipment such as cage washers and autoclaves. Strong evidence of the continued need for this program is given by the large number of highly meritorious applications that could not be funded each year since the program was initiated in 1985.

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The need for veterinarians trained in the specialty of laboratory animal medicine and research continues to be a pressing issue. In FY 1989, the Laboratory Animal Sciences Program supported the training of 66 post-graduate veterinarians in 16 institutional programs and three veterinarians through individual fellowships. Graduates of these programs have distinguished themselves by receiving Special Emphasis Research Career Awards, individual research honors as junior investigators, and positions of leadership in animal care programs at prestigious research institutions.

The major objective of the Diagnostic and Investigative Laboratories is to develop new laboratory animal models of human disease and to improve laboratory animal health through research projects. The latter is particularly important as valuable animals such as transgenic and immunodeficient animals, with unique susceptibilities to disease, represent an increasingly important part of the laboratory animal population. One such study was that of mouse hepatitis virus (MHV), a serious, widespread, and very contagious disease of mice. MHV, often in a latent state, can invalidate research results because of its effect on the immune system. There is presently no method to insure protection for mice against this disease. Investigators at Yale University, working with monoclonal antibodies to the tissue receptor for MHV, have shown that administration of the antibody to infant mice limits the spread of the virus in infected mice and may be effective against different strains of the virus.

Animal models which have been helpful in studies on the etiology, pathogenesis, and treatment of infectious, genetic, and malignant human diseases include a wide variety of species. In FY 1989, seven animal model and special colony projects involving studies on diseases of rodents, rabbits, cats, dogs, cattle, ferrets, and nonhuman primates were supported. One study involved a strain of mice with a mutation causing abnormal fatty acid metabolism. Similar disorders in humans may be much more common than those related to abnormal phenylalanine metabolism which result in phenylketonuria and has an estimated prevalence of only 1 in 12,000. Further investigations with this mouse model have been conducted in the areas of gene therapy and have included factors such as diet, drugs, and infectious diseases, which may exacerbate the condition. These studies will benefit humans with similar problems.

The Laboratory Animal Sciences Program supported several nonhuman primate colonies to ensure the continued availability of these animals for research use and to investigate their unique characteristics, genetics, and diseases. The Caribbean Primate Research Center (CPRC) has a large colony of rhesus monkeys with the most complete life history information of any nonhuman primate population in the world. The CPRC provides a resource for research studies on obesity, diabetes mellitus, hypertension, pathology of joints and bones, and ocular diseases.

Four reference centers provide special animal tissues, coordinate the exchange of nonhuman primates and their tissue among research institutes, conduct workshops, and publish scientific and technical information in the field of laboratory animal medicine. Many investigators benefit from these resources yearly.

Regional Primate Research Centers Program

The seven Regional Primate Research Centers were established 30 years ago to provide specialized facilities for research using nonhuman primate resources, including experienced personnel and appropriate research environments. Their research focuses on mechanisms and processes underlying human diseases and health problems. Each regional center has close administrative and research relationships with its host academic institution and is staffed with a multidisciplinary group of core biomedical scientists, usually holding appointments at the Center's host academic institution.

The Centers have a secondary role of helping to assure the availability of a wide variety of nonhuman primate species. Research is conducted by core scientific staffs, as well as collaborative and affiliated investigators from other institutions who use the laboratories and primate resources. Collectively, the seven Centers maintain over 15,500 primate animals, representing 29 species, and provide resources and services for over 1,300 scientists.

Investigators at the Oregon Regional Primate Research Center fed diets which were very low in omega-3 fatty acids to rhesus monkeys during pregnancy and to their infants from birth. In deficient infants, the amounts of omega-3 fatty acids in the brain and retina were greatly reduced, visual acuity was reduced by 50% at 2 to 3 months of age, and the retina showed abnormal physiological responses to light. Differences in the behavior of deficient monkeys, including increased stereotyped behaviors and increases in repeated errors in a learning task have now been found. Furthermore, deficient monkeys show abnormally high fluid intake and excretion. The underlying physiological or behavioral reasons for this effect are now being studied.

A team of investigators at the Washington Regional Primate Research Center have taken a major step toward the development of artificial blood vessels to bypass or replace segments of arteries blocked by atherosclerosis. A baboon model has been used to study the effectiveness and causes of failure of artificial vessels made of different materials. Grafts made of new porous materials are now being tested in patients with arterial blockage caused by atherosclerosis.

Investigators at the New England Regional Primate Research Center are studying the neurological mechanisms underlying the detrimental behavioral effects caused by cocaine abuse. They have identified specific recognition sites for cocaine in brain tissue of nonhuman primates. Studies with a large number of cocaine-like drugs have demonstrated that cocaine recognition sites are associated with the transport system for dopamine. Parallel behavioral studies in nonhuman primates have shown a close correlation between the affinities of drugs for cocaine recognition sites and their potencies for producing increased psychomotor-stimulant activity and abuse response. Their findings have strong implications for developing improved therapeutic approaches for the management of cocaine abuse.

A team of investigators at the Delta Regional Primate Research Center has recently developed a prototype vaccine, made from a virus that infects

rhesus monkeys, that has prevented the animals from becoming infected with simian AIDS (SAIDS). This achievement provides the most encouraging evidence so far that a vaccine to protect against human AIDS is indeed possible. Also, the monkeys protected by the vaccine now give researchers a rare opportunity to study an AIDS-resistant immune system to characterize the biological features responsible for preventing infection. The ability of the vaccine to protect eight out of nine monkeys is "unambiguous proof" that this vaccine strategy used in animals can serve as the basis for development of an AIDS vaccine for people. The research team made their vaccine by inactivating whole simian immuno-deficiency virus (SIV) which causes SAIDS in rhesus monkeys, and shares about 40 percent of its genetic makeup with the human immunodeficiency virus (HIV). Before such a vaccine approach can be considered in humans, further experimentation will be necessary and the safety of the vaccine must be thoroughly evaluated.

Genetic studies conducted at the New England, Delta and Yerkes Regional Primate Research Centers have provided important clues to the origin of one of the human AIDS viruses, HIV-2. Sooty mangabey monkeys naturally harbor a virus (called SIVsmm) that is very similar to HIV-2 at the genetic level. Furthermore, the natural habitat of sooty mangabey monkeys is the coastal forest region of west Africa (Senegal to Ghana), exactly the same region where HIV-2 is endemic. These and other findings indicate that sooty mangabey monkeys may be the source of cross-species infection of humans and the origin of HIV-2 in West Africa. A search for potential candidates as the origin of HIV-1 are under study, but none has been identified thus far.

Chimpanzee Breeding and Research

The Chimpanzee Breeding and Research Program (CBRP) is designed to provide a stable supply of healthy chimpanzees for biomedical research and to perpetuate the chimpanzee population in the United States. This is the first and only nationwide program to bring the expertise and experience of chimpanzee breeders and researchers together in a unified endeavor. There are currently 431 disease-free breeding chimpanzees in the Program's colonies, and a total of 147 live births have been produced since inception of the program. At the present time the CBRP is growing at a rate of 5 percent a year.

Their unique physiologic and genetic similarities to humans make chimpanzees the best animal models for some of the most devastating human diseases. For example, the chimpanzee plays an important role in two very serious health threats: Hepatitis C and AIDS (caused by the human immunodeficiency virus, HIV). Animal model development efforts for the study of human diseases such as leprosy and tuberculosis are also in progress. Immunological and virological studies to pursue these insidious diseases have already been initiated. The close immunological and physiological similarities of chimpanzees to humans make these animals especially valuable for studies designed to evaluate the safety and efficacy of new and powerful pharmaceutical agents.

Specific Pathogen Free Rhesus Breeding and Research

The Specific Pathogen Free (SPF) Rhesus Breeding and Research Program was established to create self-sustaining rhesus breeding colonies which are

free from contamination with certain simian retroviruses and herpes B virus. This is the first nationwide effort to ensure the development of a stable population of SPF rhesus monkeys. In addition to providing SPF animals to the biomedical community, the program supports research to enhance the quality of a well-defined animal by development of better diagnostic tests for retroviruses and herpes B infection; improved housing and husbandry practices (environmental enrichment); computerized record systems; and new techniques which permit in-depth genetic monitoring. There is a critical need to assure that an adequate supply of SPF rhesus monkeys is made available for use in research to develop vaccines and therapeutic agents for AIDS.

Rationale for the Budget Request

The 1991 budget request for the Laboratory Animal Sciences and Primate Research (LASPR) Program is $68,563,000. This will enable the Division to maintain support for 7 regional primate research centers; 35 laboratory animal sciences center grants; 5 chimpanzee breeding centers; approximately 23 resource-related research grants and conference grants; 9 research career awards; 37 animal facility improvement awards; 2 small business innovative research grants; and 3 research and development contracts.

The 1991 request for research training in laboratory animal sciences is $2,493,000, the same as the comparable 1990 level. This will provide support for 6 individual fellowships and 69 institutional trainees. This level of postdoctoral training is expected to provide an adequate number of well trained laboratory animal veterinarians who are urgently needed by biomedical institutions conducting animal related research.

Within the funds requested for the Regional Primate Research Centers, $3,000,000 will be available in 1991 to continue to address the repair and renovation needs of the seven Centers. This initiative was begun in 1984 to upgrade the animal facilities and maintain standards for accreditation by the American Association for Accreditation of Laboratory Animal Care. The $3,000,000 in 1991 will be used to improve sewage disposal systems, renovate ventilation and sanitation equipment, provide additional caging and cage washing equipment, and replace obsolete central research equipment.

The animal facilities improvement grant program is funded at a level of $10,931,000 in 1991. It is anticipated that approximately 37 animal facility improvement awards will be made in 1991.

The 1991 request will allow the LASPR program to maintain its research efforts directed toward the development of high quality animal resources programs; the further development of animal models and colonies; the establishment of improved nonhuman primate breeding methods; and the provision of diagnostic laboratories, reference centers and the primate information clearinghouse.

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Impact Data	1990 Appropriation	1991 Estimate	Increase or Decrease
Primate research centers	$37,129,000	$37,541,000	+$412,0000
Laboratory animal sciences	30.742.000	31.022.000	+280.000
Total	67,871,000	68,563,000	+692,000
Research centers			
Number	47	47	---
Amount	49,091,000	49,701,000	+610,000
Other Research			
Number	76	76	---
Amount	15,574,000	15,631,000	+57,000
Training			
FTTP	75	75	---
Amount	2,493,000	2,493,000	---
Research & Development Contracts			
Number	2	2	---
Amount	713,000	738,000	+25,000
Total	67,871,000	68,563,000	+692,000

Research Resources

Biomedical Research Support

Authorization: Indefinite.

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$78,788,000	$52,966,000	-$25,822,000

Purpose and Method of Operation Program

The Biomedical Research Support (BRS) Program is designed to strengthen institutional research in the health sciences. It consists of three subactivities, the Biomedical Research Support Grant Program, the Shared Instrumentation Grant Program, and the Minority High School Student Research Apprentice Program. Each of these subactivities is described below.

Biomedical Research Support Grant Program

The objective of the Biomedical Research Support Grant (BRSG) Program is to strengthen, balance and stabilize the biomedical research infrastructure of institutions actively engaged in health-related research. The program provides flexible funds on a formula basis to institutions to support biomedical research needs not served by other support programs and for purposes that are best described at the local level by grantee institutions. Consistent with the Secretary's Minority Health initiatives, in 1991, one-third of the BRSG funds will be awarded to institutions to increase support for underrepresented minorities or economically disadvantaged people. Examples of the uses of BRSG funds reported by grantees are:

- Support for Young Investigators: BRSG funds are used to support the recruitment of new faculty, to help establish their laboratories and as seed money to develop highly competitive extramural grant applications. In FY 1987 and FY 1988 over 130 investigators who had previously received BRSG support were awarded five-year FIRST awards.

- Pilot Studies: The BRSG Program is widely recognized as a prime source for supporting new, novel and innovative research ideas which are in early stages of investigation, before they have reached a suitable stage to compete for NIH funding. The program supports the undertaking of new ventures and the development of new, emerging research technologies. In FY 1989, for example, BRSG funds supported 143 small projects on AIDS and 273 projects on the mapping of human and complex genomes.

- Interim Support: BRSG funds provide bridge funding and salary support when necessary and provide continuity to research projects that might otherwise go through expensive shut-down and start-up procedures.

- Central Resources: BRSG funds are used to support shared core facilities such as tissue culture and hybridoma facilities as well as to upgrade animal facilities to achieve compliance with Federal animal welfare regulations.

In FY 1989, the BRSG program awarded $55.2 million to support more than 8000 pilot and small research projects at 633 institutions.

The program provides no indirect costs, decentralizes research support decisions that need not be made by NIH staff and allows management decisions to be made by grantee institutions with a major saving of time and overhead expenses.

The most distinguishing feature of the program is the opportunity provided for grantee institutions to exercise on-site judgment regarding emphasis, specific direction, and content of activities supported, thus enabling the institution to respond quickly and effectively to emerging opportunities and unpredictable requirements, to enhance creativity, to encourage innovation, to provide for pilot studies, and to improve research resources, both physical and human.

According to Dr. Jack H. Mendelson, a physician at the Alcohol and Drug Abuse Research Center at the McLean Hospital in Belmont, Massachusetts, BRSG support was absolutely essential in carrying out a preclinical evaluation of buprenorphine, a pain reliever. The study showed that rhesus monkeys that had been self-administering cocaine stopped administering cocaine, but not food, upon receiving buprenorphine. There were no serious side effects or withdrawal problems, raising the possibility that buprenorphine might hold prospects for being a new addiction-fighting medication which may help wean humans from both cocaine and heroin. BRSG funds were used to bring the animal facilities into compliance with federal regulations.

The availability of BRSG "bridging" support made it possible to keep a unique 20-year longitudinal study of the independently living, rural elderly, started in 1968, alive during a temporary hiatus in extramural funding. The study was carried out by Dr. Richard H. Hessler at the University of Missouri at Columbia. By 1986, only 185 of the original 1,700 were still living and they were growing older. The youngest subject was 85 years of age. BRSG funds were awarded which allowed, without delay, interviewing of the oldest 30 people in the cohort--those that were clearly at the greatest risk of mortality. All of these subjects were 94 or older. Subsequent to this, an award was made to continue this work by the National Institute of Aging. Thus, BRSG funds provided timely interim support of this unique sociological study.

Dr. Hie-Won L. Hann, Professor of Medicine at Jefferson Medical College in Philadelphia, Pennsylvania studied the involvement of iron in tumor growth by monitoring the effect of nutritional iron deficiency on the growth

of transplanted tumor cells in mice. The results suggest that iron deficiency decreases the growth rate of tumors in mice; or that tumor cells grow better in an iron-rich environment, a finding which should be considered when designing treatment for patients with cancer. Iron oversupply may enhance tumor growth and adversely affect cancer therapy. BRSG funds were used to purchase new and upgraded caging for the central animal facility. The specialized caging was necessary for the isolation of the mice and for facility requirements for the humane care and use of animals.

BRS - Shared Instrumentation Grant Program (SIG)

Progress in medical research depends heavily upon instruments; many advances in basic and clinical research have been possible only because advances in instrumentation have opened up new ways to conduct scientific research.

Recognizing that a lack of funds for purchase of equipment can hamper biomedical research, the DRR implemented the Biomedical Research Support-Shared Instrumentation Grant (SIG) Program in 1982 to help institutions buy new instruments and upgrade older equipment. The SIG program supports instruments that cost more than $100,000. The maximum award is $400,000 and the equipment must be shared by three or more PHS supported investigators at an institution. Instruments supported include a wide variety of commercially available instruments such as nuclear magnetic resonance, electron paramagnetic resonance, X-ray and mass spectrometers. These instruments coupled with various separation technologies have revolutionized the nature of the problem on which biomedical researchers work.

Keeping research institutions well-stocked with either state-of-the-art or routine instruments is becoming more of a burdensome problem. New equipment is generally very expensive and at the rapid rate that new technologies appear on the market, existing instruments, even those recently acquired, are apt to be rendered obsolete.

The growing need for instrumentation is reflected in a recent surge of applications. In both 1989 and 1990, the SIG program received more than 400 applications - nearly twice the number it received in its inaugural year. The funds requested, which had risen steadily from $39 million in 1982 to $64 million in 1988, rose to over $100 million in 1989 and 1990.

A protein microsequencer, an amino acid analyzer and a DNA synthesizer purchased with funds from the SIG Program were critical to the recent breakthroughs on the brain amyloid protein and the sequencing of the gene in mammals and humans with Alzheimer's disease. The protein that forms plaques in the brains of patients with Alzheimer's disease has been found for the first time elsewhere in the bodies of these patients--in their skin, the tissues just beneath the skin, blood vessels and the intestines. This discovery could lead to the development of a practical diagnostic test for the estimated 2 million Americans with this disease, a test that could also prove useful in monitoring the course of the disease and judging the effectiveness of experimental treatments. Dr. Dennis J. Selkoe, who made the discovery during the studies conducted at the Brigham and Women's Hospital in Boston, Massachusetts, claims the protein, called amyloid beta

protein, might have to be transported to the brain from elsewhere in the body. If so, blocking this protein from entering the brain might prevent or halt the progress of Alzheimer's disease.

Using a coupled plasma mass spectrometer funded by the SIG Program, investigators at the Clinical Nutrition Research Unit at the University of Chicago have developed, for the first time, a novel isotopic tracer method to study iron metabolism in infants. Despite the risk for developing iron deficiency there is little quantitative data available about the extent of iron absorption in infants and the effects of various dietary components. Since the development of this novel approach, studies have been carried out with infants and children of various ages. These are the first studies to provide quantitative data on this aspect of iron metabolism in infants and children and will help to define iron requirements of this age group.

SIG funds were awarded to Dr. Catherine Chew and other NIH supported investigators at the Morehouse School of Medicine in Atlanta, Georgia to purchase a mini-computer-based digitized video image analysis system which allows the visualization of a variety of activities in living cells maintained on a microscope stage. The image analysis system has allowed the development and characterization of the first ever hormonally-responsive cultured gastric parietal cell preparation. Parietal cells are the acid-secreting cells in the stomach. There is a well-established relationship between acid secretion and duodenal ulcers. Treatment of ulcers has improved in the past decade due to the development of drugs such as tagamet (cimetidine) which inhibit gastric acid secretion by blocking the stimulatory action of histamine on H_2-type receptors. Not all ulcers respond well to treatment, however, and these drugs have side-effects. An increased knowledge of the factors controlling parietal cell acid secretion will lead to improved diagnosis and treatment of ulcers.

Minority High School Student Research Apprentice Program (MHSSRAP)

Changing demographics predict that more minority representation will be needed in the health care professions, both on the level of the health science researcher and the level of practicing physician.

The MHSSRAP looks to the year 2000 by continuing its efforts to make the choice of the health care professions and health research a viable reality for an increasing number of students from underrepresented minority groups. The MHSSRAP plays an integral role in motivating and inciting interest in science by providing minority high school students with eight weeks of hands-on experience in basic and clinical laboratories across the country. In FY 1989, the MHSSRAP awarded $1,674,000 to 348 major research/training institutions that were responsible for recruiting and assigning students to experienced, sensitive mentors. An estimated 1,116 students participated in the program in FY 1989 bringing the total number of students supported since the program began in 1980 to 8,070.

Most of the students are juniors (50%) or seniors (33%). The program is reaching different minority groups: 55% of the students are Black, 17% Hispanic, 22% Asian, 3% American Indian, and 3% are classified as other. The program is reaching both male (40%) and female (60%) high school students. Other positive outcomes include: (1) 54% of the students report

that the program helped them to develop an interest in a research career; (2) most students have enrolled in college, university or professional schools leading to careers in the health sciences, and some students have graduated from medical school or graduate school; (3) one student, Ana Pavich of Long Island City, New York, was one of 40 high school seniors selected as a winner in the Science Talent Search, a national contest sponsored by the Westinghouse Electric Corporation and Science Service.

Rationale for the Budget Request

The 1991 budget request for the three components of the Biomedical Research Support Program is $52,966,000.

The Biomedical Research Support Grant (BRSG) formula activity will be funded at a level of $17,700,000. To assist in the national mission to increase the numbers of women, underrepresented minorities, economically disadvantaged people, and others in science and engineering, one-third of the funds will be awarded to institutions to increase support for underrepresented minorities or economically disadvantaged students.

In 1991, approximately 670 grant awards will be made, about the same number as 1990. These funds will be awarded using a formula system similar to that used in previous years. Eligibility to receive funds in this program requires that the applicant institution have received at least three PHS research grants, valued at least $200,000 in 1990. The resulting awards will average approximately $27,200 each, a reduction of $41,000 from 1990.

This level will also enable the Division to support at least 137 Shared Instrumentation Grants (SIG) for a total of $32,620,000. This amount represents an increase of $27,000 from the FY 1990 level. Eligibility to compete in this program requires that the applicant institution have received at a BRSG grant in 1990. This program is designed to replenish and maintain the large scale, expensive, shared instrumentation necessary for biomedical research.

The Minority High School Student Research Apprentice Program (MHSSRAP) program will be continued in 1991 at a level of $2,646,000, an increase of $836,000 over 1990. At this level of funding, the Division will provide summer research apprentice support to about 1,764 high school students around the nation. Eligibility to compete in this program requires that the applicant institution have received a BRSG grant or an MBRS grant in 1990. These summer experiences in various aspects of health-related research will attract some of the apprentices to higher education and careers in health research.

Impact Data	1990 Appropriation No.	1990 Appropriation Amount	1991 Estimate No.	1991 Estimate Amount	Increase or Decrease No.	Increase or Decrease Amount
Biomedical research support	653	$44,385,000	673	$17,700,000	+20	-$26,685,000
Minority high school student research apprentice	---	1,810,000	---	2,646,000	---	+836,000
Shared instrumentation grants	137	32,593,000	137	32,620,000	---	+27,000
Total	790	78,788,000	810	52,966,000	+20	-25,822,000

Research Resources

Biological Models and Materials Research

Authorization: Indefinite.

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$5,364,000	$5,356,000	-$8,000

Purpose and Method of Operation

The Biological Models and Materials Research (BMMR) Program provides for the development and support of nonmammalian models for biomedical research, and provides critical biological materials to the research community. The BMMR program is the focal point for the development of nonmammalian model systems, such as invertebrates, lower vertebrates, cell systems and nonbiological systems for biomedical research. The Program supports its activities through research centers, research contracts, and investigator-initiated research grants.

The BMMR Program supports several resource centers that acquire, authenticate, maintain, and distribute a large and varied number of lower organisms and biological materials to the research community. These resources are indispensable to investigators in a wide range of research areas, including the complex genome project. The genome project, which includes the mapping and sequencing of the human genome, has other aspects, such as the analysis of pertinent model genomes, the development of diagnostic tests, and the prevention and treatment of human disease. The Repository of Human DNA Probes and Libraries, part of the American Type Culture Collection (ATCC), maintains and distributes cloned genes, and DNA probes and human chromosome libraries, all of which are important tools in the genome project and molecular genetics in general. The Caenorhabditis Genetics Center and the Yeast Genetic Stock Center provide important well-defined model organisms, nematodes and yeast, respectively, which will contribute new technologies and improved understanding of genome structure through comparative studies.

The American Type Culture Collection (ATCC) distributes over 100,000 microorganisms, including bacteria, viruses, fungi, and hybridomas and cell lines to the research community. Investigators have introduced a retrovirus vector into cells, available at the ATCC, to generate a cell line that produces the retrovirus vector in large amounts. The vector was then used to mark tumor infiltrating T-lymphocytes from a patient with melanoma. The cells were returned to the patient, and the fate of the cells will provide important information for gene transfer studies in humans.

The National Disease Research Interchange (NDRI) procures and distributes normal and diseased human tissues and organs to researchers interested in studying human systems directly. Using this resource, investigators have designed methods for the isolation and preservation of human pancreatic islet cells. In turn, these investigators have provided other researchers with islet cells for diabetes research. For example, investigators found that arachidonic acid is metabolized within human pancreatic islets to metabolites for possible modulation of glucose-induced insulin secretion. Also, researchers have isolated and characterized human islet cell complex glycolipids which appear to be targets for autoantibodies in patients with Type 1 diabetes.

The BMMR Program has been the focal point for activities involved with the Congressional intention to reduce or replace the use of vertebrate animals in research by supporting the use of nonmammalian models for biomedical research, and by issuing Program Announcements (PA) for the past three years and a request for applications (RFA) this year for the solicitation of applications in this area. These PAs have produced much interest from the research community. Congress also requested an evaluation of nontraditional animal models. In response, a conference on this topic, organized by BMMR Program staff and two other BIDs, was held in May 1989, and a synopsis of the conference will be published in a national scientific journal in 1990.

Many investigators cannot produce large quantities of cells necessary for their research projects. The MIT Cell Culture Center provides researchers with custom-produced cells to fit their needs. This resource provided cells to investigators that resulted in the characterization of a glycoprotein, sialophorin, which is defective on lymphocytes of patients with Wiskott-Aldrich syndrome, an X chromosome-linked immunodeficiency disease, and in the identification of a cell adhesion molecule that is the major surface receptor for rhinoviruses which cause the common cold. Investigators have demonstrated how the HIV enhancer in T lymphocytes is activated by an initiation factor which is found in many viruses. The Center is providing cells to researchers to characterize this factor. Progress on many areas of immunology and molecular biology will enhance our knowledge of the mechanism of diseases such as AIDS.

The BMMR Program supports activities that are involved in the construction of a framework or matrix for the organization of biological knowledge, or Bio-Matrix. A conference was held in August 1989 to assess the feasibility of the Bio-Matrix concept. Investigators are developing a means to connect biological data bases systematically so that researchers can access and analyze existing biosequence information, especially with respect to molecular structure/function relationships in gene expression.

Investigators are testing the utility of qualitative models for gene expression by modeling the life cycle of HIV. Information from this type of modeling will be useful in solving problems in molecular biology, such as understanding the effects of regulatory proteins on HIV gene expression.

Rationale for the Budget Request

The FY 1991 budget request for the Biological Models and Materials Research (BMMR) Program is $5,356,000, a decrease of $8,000 from the comparable FY 1990 level. This will enable the Division to support 4 noncompeting research project grants, 6 research centers, 7 resource-related research grants and conference grants, and 3 contracts.

The 1990 request will allow the BMMR Program to maintain its program of research directed toward exploring the development of non-mammalian model systems for biomedical research, and to continue to support the availability of critical biological materials, such as cell systems and lower organisms, for use in research.

Impact Data	1990 Appropriation	1991 Estimate	Increase or Decrease
Research Project Grants			
Number	4	4	---
Amount	$749,000	$787,000	+$38,000
Research Centers			
Number	6	6	---
Amount	1,342,000	1,342,000	---
Other Research			
Number	7	7	---
Amount	1,337,000	1,343,000	+6,000
Research and Development Contracts			
Number	3	3	---
Amount	1,936,000	1,884,000	-52,000
Total	5,364,000	5,356,000	-8,000

Research Resources

Research Centers in Minority Institutions Program

Authorization: Indefinite.

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$17,503,000	$22,833,000	+$5,330,000

Purpose and Method of Operation

Congressionally mandated in 1985, the Research Centers in Minority Institutions (RCMI) Program objective is to expand the Nation's capacity for research in the health sciences by assisting, through grant support, predominantly minority institutions that offer the doctorate degree in the health sciences or health-related sciences to improve their research infrastructure.

To date, seventeen institutions have received awards. The institutions that have received RCMI awards include three colleges of pharmacy, seven medical schools, six graduate schools and one school of veterinary medicine. They are located in the states of Hawaii, California, Texas, Louisiana, Tennessee, Georgia, Alabama, Florida and New York, as well as in Puerto Rico and Washington, D.C. Program awards have already expanded the biomedical research capacity of grantee institutions.

In FY 1989, five supplemental awards were made to develop a research infrastructure for AIDS and AIDS-related research. This is an important funding mechanism for the RCMI Program, since AIDS has such a disproportionate impact on minority populations. According to the Center for Disease Control HIV/AIDS Surveillance Report of October, 1989, 47,591 of 109,167 cases of AIDS or 43.6% of the cases reported to date are Black, Hispanic, Asian/Pacific Islanders and Mexican Indian/Alaskan Natives. RCMI grantee institutions are located in the midst of these populations. This coupled to their historical role in addressing health problems and issues that affect these populations, positions them to play a major role in addressing this problem in these populations. In response to the FY 1989 congressional mandate to the BIDs of NIH, the NIAID cofunded this initiative. It is anticipated that this support mechanism will enable RCMI grantees to make major contributions in understanding the infectivity of the AIDS virus. A case in point is the establishment of immortalized cultures of human retinal pigment epithelial cells on collagen gels using protooncogenes. Using this system, scientists at the Morehouse School of Medicine in Atlanta, Georgia, have determined that the human immunodeficiency virus (HIV) replicates in these cells after transfection.

The system is now being used as a model to investigate how HIV infection modulates the expression in the tissues of cytomegalovirus, a major cause of blindness in AIDS patients.

Recently biomedical scientists discovered the central role of the major histocompatibility complex (MHC) in controlling and regulating the immune response. In humans the products of this gene complex are called human leukocyte antigens (HLA) because of their initial detection on white blood cells. Historical interest in HLA has been based on the role of these antigens in transplant rejection. However, current interest in these cell membrane products transcends the boundaries of conventional transplantation immunology because of increasing knowledge of the broader aspects of HLA as cell-surface receptors that regulate immunoresponsiveness and susceptibility to a variety of chronic debilitating diseases of unknown etiology. In addition to clearer insight into the complex and intricate details of self-recognition at the molecular level, a better understanding of the role of HLA immunogenetics in disease susceptibility offers new prospects for diagnosis, prevention, and treatment of HLA-associated diseases.

An RCMI award to Howard University in Washington, D.C., in September 1985 includes support for a human immunogenetics laboratory. This laboratory now plays a key role in defining HLA phenotypes that facilitate better tissue matching between donor and recipients in organ transplantation. The greater the degree of HLA compatibility, the less immunosuppression needed to prevent rejection of the transplant. Numerous studies have shown that HLA matching improves the long-term survival of transplanted organs. In addition to serological definition of HLA phenotypes, this laboratory utilizes new techniques for studying specific DNA sequences to define HLA genotypes in various groups of patients with HLA-associated diseases. While the tremendous diversity in HLA observed in American Blacks can complicate tissue matching for organ transplantation, it is a valuable tool for dissecting the role of HLA genes in immunoregulation and disease susceptibility.

Among the important findings that have emerged from the Howard University immunogenetics laboratory are those on the unique HLA-D region heterogeneity of Blacks. In a recent publication of work presented at the XII International Congress of Transplantation Society held in Sydney, Australia, in 1988, a Howard University researcher showed how HLA-DR3, DQ heterogeneity in American Blacks was useds to determine the association of HLA-DQ with disease susceptibility and resistance to insulin in insulin-dependent diabetes mellitus.

Rationale for the Budget Request

The FY 1991 budget request for the Research Centers in Minority Institutions (RCMI) is $22,833,000, a 30 percent increase over the FY 1990 appropriation for this program. The increase for this program responds to the Administration's priority to increase programs directed at underrepresented minorities and disadvantaged persons, and will be used to further the goals of the RCMI program to enhance the health research capabilities of minority institutions.

The increase in the RCMI program will allow for an increased emphasis on research in ethnic-specific diseases, expanded involvement in AIDS clinical trials, enhanced collaborative efforts with nearby majority institutions and national laboratories, and support for other eligible institutions. This will be accomplished by expanding the research capacity at RCMI grantee institutions, by providing support to increase staff expertise and technical knowledge, and by upgrading scientific instrumentation available to the institutions.

The request for RCMI funding is included in the Division of Research Resources appropriation request for the first time this year. Previously funding has been provided through the Office of the Director.

Impact Data	1990 Appropriation	1991 Estimate	Increase or Decrease
Research Centers			
Number	17	20	---
Amount	$17,503,000	$22,833,000	+$5,330,000

Research Resources

Research Management and Support

Authorization: Indefinite.

Budget Authority:

1990 Appropriation		1991 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA
89	$11,433,000	90	$12,559,000	+1	+$1,126,000

Purpose and Method of Operation

The Research Management and Support activity provides the resources and staff necessary for the program management and scientific direction of the Division and its six extramural programs. Scientific and administrative staff work together to plan, develop and carry out these programs in order to provide the extramural research community with the resources essential for the conduct of biomedical research.

Administrative and managerial services are provided through the Office of the Director, the Office of Science and Health Reports, the Office of Program Planning and Evaluation, the Office of Grants and Contracts, and the Office of Administrative Management (including financial management, human resources management, information resources management, as well as provision of general administrative services to all components of DRR).

The extramural review staff provides policy direction and coordination for all phases of scientific and technical review activities within DRR involving research grants, research training grants, and research and development contracts. The extramural program staff provides the planning, development, administration and monitoring of the extramural research programs of DRR, and serves in a liaison capacity for applicants, grantees, other components of NIH and the Department, advisory bodies, and other interested groups.

In addition, the Research Management and Support activity includes funds to support the Division's use of the NIH centrally furnished services supported through the NIH management fund, the DHHS/NIH general expense fund, and the NIH service and supply fund.

Rationale for the Budget Request

The 1991 budget request for Research Management and Support is $12,559,000. This level includes $661,000 for mandatory administrative cost increases, $63,000 for the annualization of the January 1990 pay raise, and $300,000 for the FY 1991 cost of the January 1991 pay raise, and a program

increase of $102,000. This program increase will provide for additional support for activities related to the expanded programs in the Research Centers in Minority Institutions, and the Minority High School Student Research Apprentice Program.

During FY 1991 continued emphasis will be placed on management improvement and operating efficiencies. The Division will monitor travel, printing, contractual services, and the purchase of supplies and equipment, while continuing to foster efforts in office automation and streamlined administrative procedures in order to most effectively carry out the Division's mission.

NATIONAL INSTITUTES OF HEALTH

Research Resources

Detail of Permanent Positions

	1989 Actual	1990 Estimate	1991 Estimate
ES-4	2	2	2
Subtotal	2	2	2
GS/GM-15	6	7	7
GS/GM-14	13	15	16
GS/GM-13	7	6	6
GS-12	11	11	11
GS-11	4	4	4
GS-09	4	4	4
GS-08	2	4	4
GS-07	10	12	12
GS-06	12	10	10
GS-05	4	4	4
GS-04	2	2	2
GS-03	--	--	--
Subtotal	75	79	80
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	--	1	1
Director Grade	4	5	5
Full Grade	1	1	1
Assistant Grade	1	1	1
Subtotal	6	8	8
Unfilled positions, end-of-year	6	0	0
Total permanent employment, end-of-year	89	89	90

NATIONAL INSTITUTES OF HEALTH

Research Resources

New Positions Requested

		1991	
Research Management and Support	Grade	Number	Annual Salary
Health Scientist Administrator.....	GS-14	1	$50,342
		1	

Research Resources

Advisory and Assistance Services

The FY 1991 Advisory and Assistance Services (AAS) estimate for the Division of Research Resources is $339,000.

The contractual services estimate includes $318,000 for services obtained under purchase orders for advice and consultation in the following program areas: Laboratory Animal Sciences and Primate Research, Biological Models and Materials Research, Biomedical Research Support, Biomedical Research Technology, Clinical Research and Research Centers in Minority Institutions. Advisory and Assistance Services are additionally planned for the Office of Review and the Office of Science and Health Reports.

The FY 1991 estimate for compensation of National Advisory Research Resources Council members is $21,000.

In FY 1991, the increase required ($11,000) reflects the effects of inflation and the requirements of the programs under a stable budget.

Internal Controls

Policy guidelines exist in the form of OMB Circular A-120 and DHHS General Administration Manual 8-15. Each year a consultant services plan is prepared identifying planned AAS procurement. The NIH accounting system contains Common Account Numbers (CANs) that have been designated for use in identifying and aggregating costs for AAS.

MONDAY, MARCH 19, 1990.

NATIONAL LIBRARY OF MEDICINE

WITNESSES

DR. DONALD A. B. LINDBERG, DIRECTOR

DR. WILLIAM F. RAUB, ACTING DIRECTOR, NIH

KENT A. SMITH, DEPUTY DIRECTOR, NLM

DR. HAROLD M. SCHOOLMAN, DEPUTY DIRECTOR FOR RESEARCH AND EDUCATION, NLM

KENNETH G. CARNEY, EXECUTIVE OFFICER, NLM

SUSAN U. LEVINE, BUDGET OFFICER, NLM

DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DHHS

Mr. NATCHER. At this time we take up the National Library of Medicine. We have before the committee Dr. Donald A. B. Lindberg. Dr. Lindberg, we are glad to have you here. Tell us who you have with you at the table.

Dr. LINDBERG. On my far left is Ken Carney, our executive officer, next to him, Ms. Sue Levine, Budget Officer, our Deputy Director, Mr. Smith; on my right is Dr. Harold Schoolman, Deputy Director for education and research and the very patient Dr. Raub and Mr. Williams.

Mr. NATCHER. Thank you very much.

Now, Dr. Lindberg, we will be pleased to hear from you.

OPENING STATEMENT

Dr. LINDBERG. Thank you, Mr. Natcher.

This has been a relatively good year for NLM and certainly an exciting one. I would like to submit formal testimony for the record and review the highlights. The Congress was able to give to NLM $3.8 million for outreach in FY 1990. The program was laid out by Dr. Michael DeBakey. He described it to you during the hearings last year. This amount of funding has at least provided us a good start. I can tell you more about it if you wish.

There are other congressional actions I should report to you. The Congress created, last year, the National Center for Biotechnology Information. This Center is to handle the data resulting from the molecular investigations including the sequencing and mapping of the genomic knowledge that is so important. We have recruited a dynamic and talented new director Dr. David Lipman. He has, in turn, recruited a staff of approximately 20 extraordinary young men and women. They have a good relationship with the human genome people. They are making good progress in managing new computer data bases and inventing new algorithms and discovering relationships, which facilitate identification.

That is cutting edge science. The Congress also created for NLM an assignment in the area of AIDS. We were told to produce a data base. That has been accomplished. It is AIDSLINE. We are now looking at ways to improve it. There are two others: AIDSTRIALS which was done with FDAA and NIAID, and AIDSDRUGS which was done in the NIAID. They are available to the public and to the medical professions. In addition, Congress gave to EPA the responsibility for a particular data base, that has to do with the systematic release of toxic chemicals. The Toxic Release Inventory, or TRI, contains a list of some 30,000 sites in the country which report releases. The data, collected by EPA, is sent to NLM and our role is to make that data available to scientists and the public. That has been accomplished.

Another congressional action at the closing of the last session created the Agency for Health Care Policy and Research to deal with outcome research of the medical treatment effectiveness program. Under the legislation NLM has two obligations. One is to coordinate the health services research information and the second is to establish an information center at NLM dealing with technology assessment in this area of health services research.

We are in accordance with the legislation, making an agreement with the new bureau director, Dr. Jarrett Clinton. That will be funded by an interagency transfer from AHCPR to NLM.

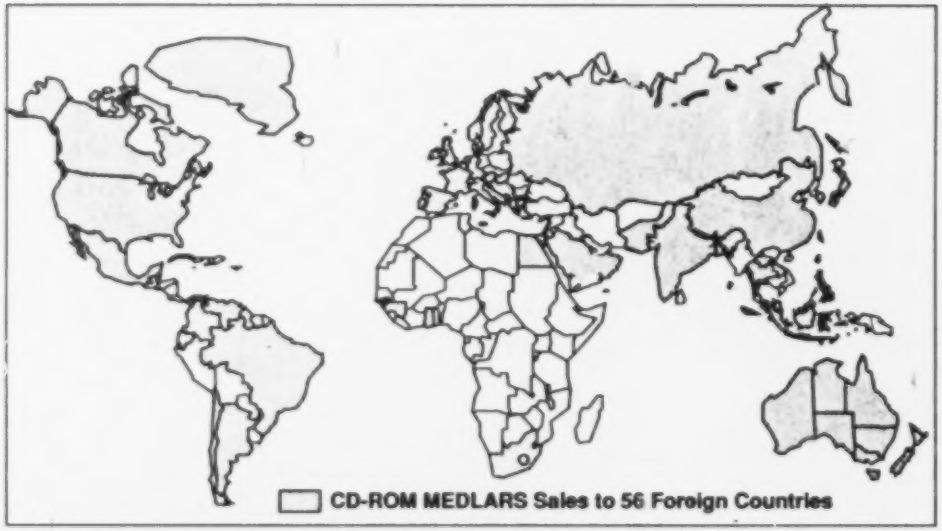
In regard to international affairs as everyone realizes, there are tremendous options now in Eastern Europe. We have had a number of visits from representatives of those countries wanting more information transfer. In some cases they are able to provide us with some useful information. Additionally the Secretary of HHS and the State Department have had preliminary discussions with the Egyptians about their idea that they want to create a National Library of Medicine in Egypt. At his request, I am leaving later this week to give them advice on the matter. I don't think I will be able to give much more than advice, but it should be an interesting trip.

Mr. Chairman, you gave us a lot of help in our preservation projects which have to do with the prevention of deterioration of the paper on which the scientific literature is printed. Our efforts are going extremely well. You will remember in 1984 it looked like tilting at windmills, a silly task but it is going very well.

Technology is improving to facilitate access to information. Our user friendly front-end system, GRATEFUL MED, is an excellent example. Every year the usage has gone up at least 50 percent. In the last 12 months the number of users has gone up 70 percent.

CD ROMs are a new storage technology. NLM creates the data base and on one of these three and one quarter inch discs you can store one year of MEDLINE. They were designed originally for the music industry and have been adapted for scientific data. We did this development through private enterprise. There were agreements with 15 companies resulting in nine products on the market. Each competes with the other and each does its own marketing re-

search to see how the medical profession wants it handled and what it will pay for the product. On the sheet before you you see a stylized map of the world and an indication of the countries where these products are sold. There are about 4000 places in 56 countries using these ROMs.



NLM charges to commercial companies:

- $5,000 for current year of Medline data (recovers cost of producing and shipping data)
- $100 for each subscription sold (recovers costs of quality assurance, retractions, errata, keying of abstracts, etc.)
- No subscription charge for products containing CATLINE, AVLINE, or MeSH data.
- No subscription charge for CD-ROM's that have link to GRATEFUL MED.
- Total revenues for FY 89 = $250,000 to U.S. Treasury

Commercial companies charge to subscribers:

- $1,000 to $1,500 annually

Dr. LINDGERG. This allows NLM to carry out information dissemination outreach functions at essentially no cost to the Government. In fact, there is yield to the Government from the license fees for those devices.

We have completed a critical incident study, which included some 1000 interviews with people who use our on line information system. The study has identified an extraordinary number and types of uses where our data bases have made a critical difference.

The highlights or the conclusions of the study are that there is an extremely wide range of use by health care professionals of these on-line systems, much wider than we imagined. They have a very strong positive effect on patient care. We heard of hundreds of examples of doctors having to treat a rare condition, in one case an abscess of the brain and they found the right treatment through the use of MEDLINE.

In another case a patient with heart failure due to a fast heart rate, as it turns out, was due to a drug from overseas not approved by FDA. No one recognized that was the cause of the affliction. That was found through MEDLINE. There are many, many dramatic examples.

The communication networks area is going very well, too. I won't give you the details at this moment. Participation in these various affairs legislatively mandated and scientifically mandated kind of strains NLM resources and imagination. We think the activities are appropriate. We welcome the challenge. We think we are contributing significantly to the forward march of science and improving health care.

I have to bring to your attention one problem. In this case it is not directly a budgetary problem but a serious problem for our institution. It is not in our written testimony. At the time the department had not taken a position on it. Now Secretary Sullivan has taken a position in agreement with NLM. Our agency supports the intent and principles of the Paperwork Reduction Act. The act is up for reauthorization under H. Res. 3695 and the companion Senate Bill, S. 742. The House bill goes far beyond the reduction of paperwork, which is a problem for us.

In the information dissemination section, it forbids agencies like ours to place any restrictions whatsoever on the use of any products created or to levy license fees or collect payments for them. There are two effects: First and probably most important, it totally destroys our quality control program. Without a legal license, there is no way we can be sure that when people put MEDLINE on CD-ROMS or tapes that they are putting them on accurately, updating them appropriately, removing errors and noting retractions, and that their software works well. Companies who deal with CD-ROMS have welcomed our agreements. They don't object. They want everybody competing with a good product.

The second effect this legislation would have is to essentially cost the Government $12,000,000. We would not be able to return $6,000,000 to the Treasury as we currently do from collections according to agreements that I believe the committee authorized, approved and endorses. We would need another $6,000,000 to pay for access related costs, including the communication network.

This legislation, from my point of view, would be very, very deleterious. Secretary Sullivan has written to Budget Director Darman taking precisely this same view.

I have told you some of the good news, and ended up with a programmatic piece of bad news. The President's request is $89,916,000 for the fiscal year 1991. I will be happy to take your questions.

Mr. NATCHER. Thank you, Doctor.

[The information follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Library of Medicine

Mr. Chairman and distinguished members, it is both a privilege and a welcome opportunity to appear before you today. The services of the National Library of Medicine (NLM) and the unparalleled collections of health science information upon which they are based are essential to both biomedical research and the delivery of health care in this country. The Library's programs exploit the latest advances in technology and information science in order to ensure access to this information by medical scientists, educators, and health care practitioners.

FY 1989 saw important advances in a number of the Library's programs. Those I will highlight today include biotechnology information, AIDS, development of a Unified Medical Language System, and outreach activities.

Biotechnology Information

The creation of the National Center for Biotechnology Information (NCBI) in 1989 reflects the high priority of the Congress on developing new information technologies to help understand the molecular process that controls health and disease. The explosion of information relating to areas such as molecular biology, biochemistry and genetics, results in the need for sophisticated information resources to serve the biomedical community including NIH's Human Genome initiative.

During FY 1989, a multi-disciplinary research group of computer scientists, molecular biologists, biochemists, physicians and structural biologists was assembled to (1) build new databases and enhance existing ones that involve genomic information, (2) develop tools for information retrieval and analysis, and (3) ensure communication of the information to the scientific community. Much has been accomplished in a very short time.

The Center is developing the GenInfo database both to provide a core of biological information about DNA and protein structures and to link with more detailed information in other databases. Also, the Center is creating "software toolkits" to facilitate information retrieval. The first such toolkit, now being used to produce a computerized map of the E. coli genome, will serve as a prototype for analyzing more complex genomes. In addition, the Center sponsors meetings, workshops, and lecture series, and supports grants and postdoctoral training.

AIDS

The Health Omnibus Program Extension of 1988 that established the National Center for Biotechnology Information also called for the NLM to establish databanks of AIDS-related information. NLM

now has a family of AIDS databases to provide access to diverse types of AIDS-related information, and an expanded and enhanced AIDS Bibliography.

The AIDSLINE bibliographic database developed in 1988 was expanded in 1989 and made accessible nationally via GRATEFUL MED, the microcomputer search package that allows users to search MEDLINE. NLM will continue to augment AIDSLINE by incorporating citations from other databases and abstracts of presentations from AIDS-related meetings.

Two new databases were quickly brought online in 1989; AIDSTRIALS, a database created in collaboration with NIAID that describes ongoing clinical trials; and AIDSDRUGS, the result of cooperation with NIAID and the Food and Drug Administration, which describes the agents being tested in those trials. The Library also continues to publish the monthly AIDS Bibliography through the Government Printing Office. A series of more specialized AIDS bibliographies on specific topics and for defined audiences will begin publication in 1990.

Coordination of AIDS-related information activities in the Public Health Service has been strengthened through the creation, in 1989, of a Panel on Information Services as part of the PHS Executive Task Force on AIDS. This Panel is co-chaired by the Director of the National AIDS Program Office and the Director of the NLM.

Unified Medical Language System

The purpose of the Unified Medical Language System (UMLS) is to develop a practical language system that will permit communication between the many and varied automated health information systems. A fundamental barrier to improved access to biomedical information has been the difference in terms used to describe similar concepts in different machine-readable files. The goal of the UMLS is not to impose a single biomedical vocabulary on all users and systems, but to make the myriad of classifications invisible to the user providing a single logical method to easily access a variety of biomedical information sources.

There was significant progress in developing the UMLS in FY 1989. The initial version of the "Metathesaurus," the central vocabulary component of the UMLS, has been developed. Meta-1, as the first version is called, will be available for distribution in mid-1990.

Among the priorities for the coming year will be the expansion of Metathesaurus' coverage of terminology related to the particular health problems under investigation by the newly created Agency for Health Care Policy and Research. NLM will be responding to its legislative mandate to work with this Agency on improving information support for health services research and policy development.

Outreach

As a result of concerns that many health professionals did not have ready and timely access to vital health information, Congress recently amended NLM's mission to add the function to "Publicize the availability of [its] products and services."

In response, the NLM Board of Regents convened a Planning Panel on Outreach. The Panel has formulated a plan to guide the Library's efforts to improve awareness of and access to its information services by American health professionals in all settings.

The Planning Panel, chaired by Dr. Michael DeBakey, issued a report in June 1989 recommending that NLM (1) utilize the Regional Medical Library (RML) network as a workforce in the field to bring NLM's products and services to the individual health professional, (2) ensure through grants and other mechanisms that local health science institutions have direct access to national biomedical information sources (3) expand its training fellowships and demonstration grants to satisfy the critical need for community-based health professionals trained in the use of modern computer and communications systems, and (4) develop new information products and services to enhance the utility of its present information resources.

The NLM is working with members of the RML network to promote availability and improve delivery of NLM's services to the Nation's health professionals, particularly in rural and underserved communities. One avenue being explored is utilizing health science libraries at historically black schools to specifically target minority information needs. In 1990, in an effort to reach rural communities NLM will fund a major outreach effort in New England and begin projects elsewhere in the country utilizing the RML network.

There have been significant improvements in online access to NLM's databases in 1989 and NLM's outreach effort includes a major expansion in FY 1990. GRATEFUL MED now provides access to more NLM databases. To date, more than 18,000 copies of GRATEFUL MED have been sold. Additionally the first Macintosh version of GRATEFUL MED was recently released. Its distribution in FY 1990 will allow access to an additional segment of the biomedical community.

In an effort to define user needs and further improve MEDLINE, a critical study was conducted to see how MEDLINE was utilized, particularly in the practicing physician setting. The results indicate the dramatic impact MEDLINE has had on decisions and actions of health professionals. Such data will be useful in developing databases and improving access methods to a broadening user community.

Also resulting in greater outreach will be the expanded program of "access grants" for community-based hospitals and strengthened support for research training, and fellowships. Resources will continue to be directed to promoting the use of

existing NLM information systems and the Library will utilize the feedback to develop new and enhanced products and services.

These highlighted programs are only some of the Library's current initiatives. The following is a brief program by program summary of other progress in FY 1989:

In FY 1989, NLM's Library Operations component celebrated the 25th anniversary of the Medical Literature Analysis and Retrieval System (MEDLARS). From its beginning in 1964 as a batch system that pioneered the use of phototypsetting technology, MEDLARS has evolved into a powerful multi-purpose biomedical information system that last year responded to 4.6 million online inquiries, distributed authoritative machine-readable data to more than 80 organizations, and produced more than 100 publications. During FY 1989, the number of active online access codes increased almost 50 percent to more than 30,000. Nearly half of these codes are issued to individual health professionals and researchers. The dramatic increase in the numbers of individuals doing online searches of NLM's databases has been stimulated by the availability and enhancement of GRATEFUL MED.

In the Toxicology Information Program, NLM helped develop a portable, computerized workstation that allows those responding to chemical emergencies to obtain information easily and quickly from databases on a compact disk, or by accessing hundreds of relevant databases provided by NLM or other U.S. information sources.

In 1989, NLM added EPA's Toxic Release Inventory (TRI) on NLM's TOXNET system for online searching. TRI contains data on the release of specific hazardous chemicals into the environment by facilities producing and using those chemicals. As a result, this information is now more easily obtainable by the general public. EPA and the Agency for Toxic Substances and Disease Registry have asked NLM to add several additional databases dealing with the properties of hazardous chemicals on TOXNET.

Recent advances in computer graphics and optical disc technology now make it feasible to build collections of three-dimensional, "living" medical images which can be rotated, examined from any angle, dissected and reassembled on the computer screen in ways which mimic the actual physical body parts; surgery can be practiced on the computer before it is undertaken on an actual patient. Researchers in NLM's Lister Hill Center are coordinating a "Visible Human" project to create a collection of three dimensional digital images representing the complete human body with all of its complex internal organs and body systems. The computer images will provide a powerful tool for teaching detailed human anatomy to health professions' students nationwide.

Our Extramural programs continue to serve as the unique Federal focal point for financial assistance to the nation's medical libraries and support of medical informatics research and research training. The authorization for Medical Library Assistance programs expires on September 30, 1990. These programs support projects conducted by medical libraries and other academic institutions. Projects range from the structured Regional Medical

Library program, to the innovative research and training grants for medical informatics, to the development of IAIMS to improve access to health information.

In conclusion, the National Library of Medicine welcomes its expanded role in the areas of biotechnology and AIDS information management and we enthusiastically support the priority Congress has placed on promoting awareness of and accessibility to the Library's products and services. The basic services of the Library serve to close the loop between past and present research results and the future scientific discoveries in the field of biomedicine. The rapid and efficient dissemination of biomedical knowledge is essential to the continued progress being made in understanding human life and the pursuit of better health.

Mr. Chairman, the FY 1991 request for the National Library of Medicine is $89,916,000. I shall be pleased to answer any questions you may have.

LINDBERG, DR. DONALD A. B.
Director, National Library of Medicine

September 21, 1933. New York, New York

Education: A.B., Biology, Amherst College, magna cum laude, 1954; M.D., College of Physicians and Surgeons; Columbia University, 1958; Sc.D., Amherst College (hon. caus.) 1979; Sc.D., State University of New York, (hon. caus.) 1987.

Professional History: 1984-present, Director, National Library of Medicine; 1988-present, Adjunct Professor of Pathology, University of Maryland School of Medicine; 1971-1984, Director, Information Science Group, University of Missouri School of Medicine; 1976-1980, Director, Health Services Research Center with Special Emphasis Health Care Technology Center, University of Missouri-Columbia; 1972-1973, Consultant for Health Sciences to Vice President for Academic Affairs; 1969-1971, Professor and Chairman, Department of Information Science, University of Missouri School of Library and Information Science; 1970-1971, Staff, Vice President for Academic Affairs, University of Missouri; 1967-1970, Director, Regional Medical Program Information Systems; 1968-1970, Staff, Executive Director for Health Affairs, University of Missouri; 1962-1970, Director, Medical Center Computer Program, University of Missouri; 1967-1969, Director, Missouri Regional Automated Electrocardiography System; 1966-1969, Associate Professor of Pathology, University of Missouri School of Medicine; 1963-1966, Assistant Professor of Pathology University of Missouri School of Medicine; 1962-1963, Instructor in Pathology, University of Missouri School of Medicine; 1960-1963, Director, Diagnostic Microbiology Laboratory, University of Missouri Medical Center; 1960-1962, Resident Physician in Pathology, University of Missouri School of Medicine; 1959-1960, Assistant Resident in Pathology, Columbia-Presbyterian Medical Center; 1958-1960, Assistant in Pathology, Columbia University College of Physicians and Surgeons; 1958-1959, Intern in Pathology, Columbia-Presbyterian Medical Center; June 1955-Sept. 1955, June 1954-Sept. 1954, Research Assistant to Dr. O.E. Schotte, Amherst College.

Honors: Phi Beta Kappa; Simpson Fellow of Amherst College (1954-1955); Markle Scholar in Academic Medicine (1964-1969); Distinguished Practitioner in Medicine, National Academies of Practice in Medicine (1983); Member, Institute of Medicine, National Academy of Sciences (1985); Fellow, American College of Medical Informatics (1985); Surgeon General's Medallion (1989); Nathan Davis Award for Outstanding Member of Executiv Branch in Career Public Service (Federal Government) (1989); Walter C. Alvarez Memorial Award, American Medical Writers Association (1989).

Professional Memberships: Sigma Xi; American Society of Clinical Pathologists; College of American Pathologists (Telecommunication Network Committee, Committee on Emerging Technology); Missouri State Medical Association; American Association for Advancement of Science; American College of Medical Informatics; Association for Computing Machines (SIGBIO); Salutis Unitas; American Association for Medical Systems and Informatics, Board of Directors; Symposium

on Computer Applications in Medical Care, Board of Directors; National Board of Medical Examiners, Board Member; Washington Society for the History of Medicine; Editor, Information Methods in Medicine, Lecture Notes in Medical Informatics, and Journal of Medical Systems; National Academy of Practice in Medicine Distinguished Practitioner; Computer Science and Engineering Board, National Academy of Sciences (1971-1974); U.S. Representative to International Medical Informatics Association, and Trustee (1975-1984); Board of Health Sciences Policy, Institute of Medicine; President, American Medical Informatics Association (1988-present).

Dr. Lindberg is the author of 4 books and more than 150 articles, reports, and chapters of monographs.

OUTREACH

Mr. NATCHER. You have requested a very modest increase for your new outreach initiative, Doctor. Why didn't this receive a higher priority in your internal budget process?

Dr. LINDBERG. Within the President's budget there really is not much of an increase. We did keep the highest priority for outreach. It does not correspond with the recommendations of Dr. DeBakey but it is the best we can do and still stay within the budget.

NLM FUNDING

Mr. NATCHER. Which activities, Doctor, will consume the major part of this funding?

Dr. LINDBERG. The total overall funding for the institution?

Mr. NATCHER. Yes.

Dr. LINDBERG. About two-thirds of all our activities are really service. They relate to maintaining and creating the collection of books, journals and so forth that form the basis of this service to both the country and to the world.

Of the remainder, perhaps 20 percent supports distribution, that is to provide access to those services and about 20 percent is pure research. In outreach, the greatest portion of the increase will go to the regional library network and to assist hospitals.

USE OF MEDLINE

Mr. NATCHER. From the MEDLINE evaluation can you tell us what percentage of health care professionals regularly use the library services?

Dr. LINDBERG. Yes. We can also see that the use increases really quite strikingly every year. I used to say 4,000,000 times a year the telephone rings as access to our on line computer system is made. Actually it will be closer to 5,000,000 this year. We know that of those 5,000,000 inquiries that over 50 percent are from patient care related professionals.

The other half, of course, is science and teaching. We think between 15 and 20 percent of American physicians are using the systems. That figure is hard to get. We know about the people who use it but not much about the people who do not.

We think we are inching up on 15 or perhaps 18 percent now. We feel badly that 100 percent don't use the system because it is paid for with public funds. We know our outreach program has to be strengthened to eliminate whatever reasons prevent health professionals from using this resource.

RURAL INFORMATION ACCESS

Mr. NATCHER. To what extent do rural doctors have access to your data base?

Dr. LINDBERG. The beauty of this particular approach has been that there is equal access literally and technologically all over the country. Our pricing is such that since we negotiate on behalf of the Government for the value added network connection, once someone places the telephone call it doesn't matter if the user is in

New York, Los Angeles, Chicago, Mississippi, or Alaska because access is absolutely equal.

There are a couple of other things that should be said about equality of access. Essentially the way the information is progressing, the better equipment one has locally at his or her desk, the better the service is really going to be.

The little modems govern how fast the information goes back and forth. You have better service if you have faster, smarter equipment locally. We want doctors and health care professionals to know that it is to their advantage to have good equipment locally because they will get better service.

The last obstacle to access is to know that the system exists. Most of our outreach program is simply to be certain that we have told our story correctly and let them know our services are available.

That is where we focus most of the activity.

MEDICAL DATA BASES

Mr. NATCHER. How many medical data bases exist which are not operated by the Library of Medicine?

Dr. LINDBERG. Well that is a hard number to come by. One summer between 1984 and 1985, NIH had a task force to determine how many computer data bases in biomedical technology NIH supported. Approximately 150 were identified, but the task force did not believe the list was complete. We studied the matter more thoroughly and discovered there were approximately 500.

So we know in that little field alone there are 500 that are very directly pertinent and we think perhaps 1000 now in total. These are really amazing numbers.

Mr. NATCHER. Doctor, are they available to users in the same way as your data systems?

Dr. LINDBERG. I think it would not be fair to say that they are as available but we have done our best to make a little electronic directory so people know that they exist. That is the first step, like the creation of a phone book. In the case of chemical and toxicological information, we have completed a project with EPA to develop a system called ANSWER. Using it, you can ask a question of the computer and it knows what to call up.

In that area there are 500 data bases. We own about 20 which we think are the most important. But there are another 480 that are important. The EPA computer can know about those 500, know the phone lines and how to get in and out of them. It is rather amazing. No one person would ever know how to operate 500 systems so the computer does that in the case of chemical spills.

Mr. NATCHER. Do most of your data bases include abstracts of articles or just their titles?

Dr. LINDBERG. In general, now there are abstracts, that is in 70 percent of the entries. Fortunately a vast majority of them are English, even in the overseas literature. That has been a big help to Americans.

Mr. NATCHER. Mr. Conte, I yield to you.

Mr. CONTE. Dr. Lindberg, it is a pleasure to see you before our committee today.

Dr. LINDBERG. Thank you, sir.

CD–ROM

Mr. CONTE. We all know your library is a world leader in developing medical information systems. Doctors all over the world have benefited from having timely, accurate information from the medical literature.

Your work is vital to both biomedical research and clinical care. Chairman Natcher and I along with the Members will see to it that you continue to make substantial progress in the coming year. I am pleased to see we are making some money here after all those years of my harping on it. The CD–ROM is a new technology for your information systems especially MEDLINE.

You showed your wares here earlier. What is the role of CD–ROM and biomedical transfer of information at libraries here and abroad?

Dr. LINDBERG. We think it is pretty useful. We don't know the full scope yet but I was enthusiastic enough to encourage all those companies to make products but not enthusiastic enough to come to the committee and ask you for the $5,000,000 investment required to lose. We kind of hedged our bets and it has worked out well so far.

The first set of products were tested in 21 American health centers. We had a conference at the end of the first year to go over their experience with the CD–ROM. The medical centers found it in general very useful. They found that students were receptive and it permitted them to bring students in as users while limiting the expense.

They paid one rental fee and they had no additional charges. They found it very good for teaching. It is obviously good in Third World countries where they don't have as good a communication system as we have in the United States.

There is only one disadvantage to it. That is obvious. You cannot change the content of the diskette. So we are encouraging a couple of companies to bring this out with GRATEFUL MED on it. Then if you do this, you can first research as much as you can on the disk, then and dial GRATEFUL MED for the update. I see that as the ideal combination.

Mr. CONTE. What impact will this have on library services, management and costs?

Dr. LINDBERG. First, it is going to require more and more technologically skilled librarians. Now they have to preside formally over these networks; there is no other way to do it. I think that increases the utility of the library to the institution. They have pretty much shown that you can reduce costs by using these CD–ROM systems at a local level but only if it is networked and the networking needs a manager and some sophistication to it.

Everything is going the same way. You have to have more skilled people if you are going to achieve the reductions in costs.

Mr. CONTE. What are the interesting features and capabilities for data base in MEDLINE and CD–ROM?

Dr. LINDBERG. I think it allows people to make mistakes without feeling the clock is ticking and they are running up a bill. That is

why the students and residents like it so much. In addition, one of these disks is an AIDS information disk. That is an interesting one. It is made by the Massachusetts Medical Society. That has MED LINE and the full text of an electronic text book of medicine about AIDS produced in the University of California at San Francisco.

It has the full text of articles. You can do a MEDLINE search, identify the article and you may be able to get the full text of that article right off the same ROM.

Dr. LINDBERG. And that is close to electronic publishing.

Mr. CONTE. Well, what does the future hold for this technology, and who are the current users of MEDLINE and CD-ROM?

Dr. LINDBERG. I think for the most part it is institutional at the moment. I would like to be able to—I would like to think that some day an ordinary private doctor could have a subscription of his own or her own, and have the ROM with GRATEFUL MED literally available on the desk.

At the moment, they are a little bit more expensive than an individual can swing, and so really, they are still institutional. They exist in partnerships, libraries, associations, and sometimes they are in schools, and they can be shared by cabling and networks, and provided that way. But it is a technology of evolution. I am sure that long before the turn of this century these devices will have increased in capacity, and decreased in price, and maybe we will get one in every doctor's office. That is what I would like.

Mr. CONTE. What is the cost?

Dr. LINDBERG. If you made them in quantities, the cost would only be $10 or $15 a piece. The way they are actually marketed right now is $1,500 a year. So that is quite an expensive subscription.

Mr. CONTE. For a doctor?

Dr. LINDBERG. Yes. They think so.

UNIFIED MEDICAL LANGUAGE SYSTEM

Mr. CONTE. Or a good dinner in Washington. If there are marketing people, tell them that they can't sell it.

Doctor, a few years ago, I remember you introduced the concept of developing a unified medical language system. What progress has been made so far, and do we have any intermediate products at this time?

Dr. LINDBERG. Well, I am very pleased that this committee did back me in that request. It was my first year as Director, and it was a personal request, and I very much appreciate the help that you gave me. It has gone very well, and early this summer, in June or July, we will have real products out being offered basically to anyone. There will be three features to what we are going to produce.

One is a—I don't want to sound unduly technical, but one is a thing called a meta-thesaurus, which is a file of the meanings taken from ordinary clinical medical speech and then matched to MeSH terms from the NLM, and ICDA terms from WHO and a number of others, including psychiatry.

So these are concepts blended together and help to translate the way a doctor would ask a question to the way the computer has to

hear it and understand it. There will be about 60,000 of these terms initially.

The second product will be a semantic net, which really lets the user understand the relationships between words. Again, I don't want it to sound more than it is, but a semantic type would be virus, let's say, and another semantic type would be a name of a disease.

Well, we know that viruses can cause a disease, but not the reverse ordinarily. That will be of use to people who do computational linguistics and computer programs that try to understand speech.

And the third part will be something that we call an information sources map. That is really along the lines of what Mr. Natcher was pointing to, where the system knows where information is, and that would be ideal for us.

I could give a simple example of that. We know that many times, doctors do search MEDLINE, and in these 5,000,000 searches, they ask a question that really should be asked of PDQ, the National Cancer Institute system for cancer protocols. A librarian would know to tell the user, but the programs aren't smart enough yet. So with this information sources map, we are really taking the first step toward programs that will be smart enough to tell you where you ought to be looking.

So I think it is really going to be a major step forward and again, I thank you for its support.

REGIONAL MEDICAL LIBRARIES

Mr. CONTE. I know, Doctor, this committee has been very interested in the NLM's new outreach effort, and I hear that there will now be a Regional Medical Library for the New England States, long in coming. What level of support does the DeBakey Panel report say is necessary for Regional Medical Libraries, and if your outreach activities succeed and increase in demand for your services, will your budget be able to handle that load?

Dr. LINDBERG. Well, the answer to the first put is a numerical one. The DeBakey Panel recommended that in 1991, we would be spending $8,700,000 a year on this RML program, and in fact, we will be able to spend only $4,000,000. We will carry forward $2.7 million and add to it $1.3 million, so I guess we will be at half the level that they recommended.

The second question had to do with the—I am sorry, I have forgotten.

INCREASED WORKLOAD IMPACT

Mr. CONTE. If your outreach activities succeed——

Dr. LINDBERG. Oh, I am sorry, you asked that if we succeeded in all this, would we be able to handle a level of inquiries, and the answer is definitely yes. That is one place where the computer technology really comes to our rescue.

We could easily do twice as many inquiries as we do right now without changing anything. I mean, the computers are that efficient. And we projected that we can handle four times the work-

load with a very minimal increase in hardware, and minimal increase in people.

NEW ENGLAND RML

Mr. CONTE. You didn't mention anything about that famous New England Regional Library.

Dr. LINDBERG. Well, we are delighted that there will be a library in New England. It seems to me that some of the other good facilities that are operating out of New York was essential. There also is an outreach program in western Massachusetts that the RLM is starting.

It turns out that there are a number of unaffiliated doctors, that is doctors who really don't have any library affiliation, sometimes don't have hospital affiliation. We want to serve them and put them on line and allow them to get reprints and so forth. We have to first enroll them in the system, and it is happening.

Mr. CONTE. Thank you, Mr. Chairman.

Mr. NATCHER. Mr. Stokes?

Mr. STOKES. Thank you, Mr. Chairman, Dr. Lindberg.

Dr. LINDBERG. Yes, sir.

HISTORICALLY BLACK INSTITUTIONS

Mr. STOKES. Doctor, last year, we discussed the availability of services such as MEDLINE and GRATEFUL MED to historically black institutions. At the time, you told me that NLM had not done all that it could to make these services available. I note that you have an initiative in this area in your fiscal year 1991 budget request. Please describe this initiative and tell us how much it will cost in fiscal year 1991.

Dr. LINDBERG. Yes, sir. We have done a number of things, but I guess I should mention to begin with that NIH's policy with respect to all grantees is to offer supplements to the awards, or add to those approved awards, minority investigators and students, and so, of course, we endorse that position and have written to all of our investigators.

We have done a couple of other things on our own that I think might be worth mentioning. There is a new program in NLM that has arisen out of our Lister Hill Center, the result really of quite a few years of having students from minority schools working with us. Now we think we know a little bit better how to do this.

But in our case, Earl Henderson has designed a system in which he will continue to work with up to five of the historically black schools. We are after undergraduate students and we want to sign them on during a sophomore year, carry them through the undergraduate program, with, of course, summer work at NLM, but also with a mentor back in their home school. We really are both enriching the infrastructure of that school with the faculty person, and we hope motivating and recruiting the youngster.

Now, as I said, the Lister Hill Center has had many of these students in the past. What they think has been wrong with the programs in the past is that, first, as soon as the young man or woman completes the program, they are, if not dazzled by the bright lights

in Washington, at least by the bright salaries, depart medicine quickly. They also stop getting educated.

In other words, it is good that they got through a bachelor's degree, but they quit. So, Henderson's idea and the other Lister Hill Center engineers, is that they want minority students in engineering, they want them going as far as they can in graduate degrees. And of course, we want to keep people interested in medicine and biomedical problems.

I am very encouraged by that particular program. At a more institutional level we have taken the advice and advantage of a friendship with Dr. David Satcher to look in detail at Meharry, to determine what would be—what is it really like, what would help, or what is reasonable for an institution as small as us to do. It is clear that in his belief, there are two areas.

One is the IAIMS program. This Integrated Academic Information Management Systems program has never had an application from Meharry. In fact we have never had an application from any of the historically black schools. There is no reason for it, but it hasn't happened.

Dr. Satcher believes that help in planning informational systems for institutions like Meharry would be the first step. We are going to get one of those applications and give whatever help we can in the development of the application.

He also wants it understood that it would be a peer review grant like any other, and believes it will qualify like any other.

The second area, and he gave it second priority, is a demonstration project having to do with our increasing the amount of information services in the environment of that school, and then measuring some outcomes. The school itself is engaged in an outreach program. That is what it really amounts to.

While we think that they could stand to improve the level of informatics in Meharry, still their view is that they are in much better shape than the people that they serve. So they are involved—and involve students by sending them out to some pretty rural communities, sending medical residents for the better part of six months for rotation in remote places. And in both cases, they need to be hooked up to information systems.

So, Dr. Satcher and a number of others in his faculty that we visited, believe that those are the two most important things that we should do, and we should do them in that sequence, and that is what we will try to do.

Now, the level of outreach effort which is in the budget is $3,800,000. A third of that is going to go to underserved areas. It has to, logically. A third of it would go if we had $10,000,000, or the $35,500,000 Dr. DeBakey recommended.

PRESERVATION OF VIDEOTAPES

Mr. STOKES. Okay. What can you tell us, Doctor, about the preservation of videotapes? I understand that they have a finite lifespan?

Dr. LINDBERG. Oh, I am sure that is right. I can think of a lot we haven't taken pains to preserve, I suppose, the ones that come around home. The interesting thing about the preservation of elec-

tronic media, Congressman Stokes, is that you end up having to preserve the equipment that they run on.

We have a lot of computer stores going back to punch cards and Royal Mac-B cards and tapes that had a very sparse density compared to ones that are used now. If you don't have the equipment to run any of these media, you don't have any way of recapturing them.

So, what most people do—Library of Congress, of course, is the leader in this—is re-record them to some more modern medium. In a way, it is pitiful, but that is the way to do it. Just as you don't keep the old celluloid film, you just redo it on a modern silver base.

AIDS

Mr. STOKES. Let me ask you this, Doctor. Are the two new AIDS data bases, AIDSTRIAL and AIDSDRUGS, fully operational at this time?

Dr. LINDBERG. They are fully operational. I think we could make them a lot nicer, but they are running.

Mr. STOKES. To what extent have they been used and how do you disseminate information about their availability?

Dr. LINDBERG. Probably the best thing we have done for the AIDS information system is that we have made it possible to get to AIDS Line through GRATEFUL MED. If you look at it in a certain way, there are more users of GRATEFUL MED than any of these other systems, so that is our user base.

In the case of AIDSDRUGS and AIDSTRIALS, it is not possible to make a direct access to those through GRATEFUL MED, and so they are not used as much as the AIDSLINE. I would say that is the first thing we could do to improve those.

Second would be the kind of outreach that is necessary in all of this, some courses at meetings, some explanation to people on how to use them. We really haven't had the funding to do that, but we have got the basic systems up and running.

NLM EMPLOYMENT

Mr. STOKES. Doctor, how many employees do you have at NLM?

Dr. LINDBERG. Approximately 540.

Mr. STOKES. What percentage of those employees are minorities?

Dr. LINDBERG. I would guess about a third. Is that correct?

Mr. CARNEY. Yes.

Mr. SMITH. That is approximately correct.

Mr. STOKES. Would you provide for me for the record a breakdown in terms of all the various grades and the numbers of minorities in each of the grades?

Dr. LINDBERG. Yes, sir.

[The information follows:]

Minority Employment

Grade level:	*Number of minorities*
02	1
03	2
04	20
05	22
06	6
07	32

08	6
09	10
10	1
11	20
12	19
13	9
14	3
15	1
Ungraded	2
Total	154

Of a total of 540 employees, 29% are minorities.

Mr. STOKES. Thank you very much, Doctor.
Thank you, Mr. Chairman.

IAIMS

Mr. NATCHER. Doctor, why is there a need for Federal funding of Integrated Academic Information Management Systems? Don't the medical centers have enough interest in these systems to finance themselves, Doctor?

Dr. LINDBERG. Well, that is an interesting question. I would say that we are a catalyst more than anything else in getting IAIMS things started. In actual fact, even in the schools where we have funded IAIMS programs, I think the schools spend an average of four or five times more school money than they do of Federal money. Our program, I think, does three important things.

First, it presents the model. We know now how to get information planning done on an institutional basis, and the schools realize that and many schools come to our meetings, even though they don't have the grants.

Second, the kind of good housekeeping seal of approval that you get from going through an NIH peer review system induces a formal level of planning in the school that just doesn't happen otherwise.

In other words, the awards are not made because one bright person writes a brilliant proposal. They are only made when a school achieves a school-wide consensus to do planning the right way. So even completing the application is a step forward.

Third, of course, if they move successfully from phase one to two to three, they do ultimately obtain sizable amounts of Federal money. Phase three programs are funded at $1,000,000 a year for up to three years, so that makes a real difference in the school.

The phase one awards are $100,000, and phase two awards are up to $400,000. They are matched by a substantial amount of school money. I think we are catalytic.

LITERATURE ACQUISITION

Mr. NATCHER. Your request for literature acquisition increases by 16 percent in 1991. Does this reflect the rising cost of materials, or an increased volume of purchases?

Dr. LINDBERG. It represents an increased cost of the materials themselves. There is some small increase in amount, but the cost of the medical literature goes up faster than the general inflation rate, in this case it is 12 percent.

CATALOGING BACKLOG

Mr. NATCHER. How large is your cataloging backlog and how does this compare to previous years?

Dr. LINDBERG. Well, that is kind of good news. We are at 8,000 volumes. It used to be 12,000, and one wonders why there would be any backlog at all, but the vast majority, 90 percent of the 8,000 is not only foreign literature, it is foreign literature that is—in obscure tongues, where we really are having difficulty even getting the translations completed. I am quite proud of our catalogers having reduced the backlog down to that level. That isn't too terrible.

AUTHORIZING STATUTES

Mr. NATCHER. Dr. Lindberg, will you be proposing any changes in the authorizing statute for medical library assistance which expires at the end of this year?

Dr. LINDBERG. It does. Probably the key elements have to do with the level of funding that is appropriate in order to begin to operate at the level that Dr. DeBakey recommends in outreach, we really would have to ask for an increase in the authorization levels over the $20,000,000 proposed at the moment.

The second question that we would ask about is the level of awards made under the MLA authorization. In the case of IAIMS, they ought to be at $1,000,000. They are capped below that at $750,000.

Mr. SMITH. Yes.

NIH DATA BANKS

Mr. NATCHER. Doctor, how many data banks are maintained by the other NIH Institutes?

Dr. LINDBERG. I would say in terms of computer data banks, by NIH per se, zero, but Dr. Raub is an authority in this matter. Many, of course, are funded by NIH, and often run by commercial companies. That is an interesting question to ask. I would say the answer is zero or close to zero.

Mr. NATCHER. Dr. Raub, go right ahead.

Dr. RAUB. Defining it the way that Dr. Lindberg did, as actually operated by one of the Institutes, I believe the zero is correct. I can't think offhand of a single instance of a data base developed and managed in-house.

On the other hand, the number of data bases that are funded through research grants or center grants maintained out there in the outside world is large. Part of that array of data bases that Dr. Lindberg was identifying that need first and foremost to have a table of contents and an index for them.

Dr. LINDBERG. Probably one of the most distinguished, the one that we run and are proud of, PDQ, is of course created by the National Cancer Institute and really is their data base. They are the subject matter experts, but I counted it with NLM, because we operate it. But it is, of course, NCI's.

Mr. NATCHER. Dr. Lindberg, we want to thank you and your associates for appearing before our committee at this time on behalf of your budget request for the fiscal year 1991. This has been a good

hearing, and we want to thank you and your associates for appearing.

Dr. LINDBERG. Thank you, Mr. Natcher.

Mr. NATCHER. The committee will now adjourn until 10:00 in the morning.

[Whereupon, at 4:35 p.m., the subcommittee recessed, to reconvene at 10:00 a.m., Tuesday, March 20, 1990.]

[The following questions were submitted to be answered for the record:]

ONLINE SYSTEMS

Mr. Natcher. What kind of fee collection system do you have for individual and institutional users of the Library's online systems?

Dr. Lindberg. Individual and institutional users of the Library's online systems have several payment options. They can be invoiced monthly, they can establish deposit accounts, or they can pay by credit card. All fees are collected by the National Technical Information Service (NTIS) which serves as the Library's billing agent.

EXTRAMURAL GRANTS

Mr. Natcher. Why is the average cost of your new extramural grants increasing by 54 percent from 1990 to 1991?

Dr. Lindberg. The appearance of such an increase is a result of an anomaly. In FY 1990, a large project was transferred to the NLM from the Division of Research Resources. This project area has been given a high priority at NIH for several years. In FY 1991 the project grant will have a competing renewal status. Therefore, the increase from 1990 to 1991 reflects NLM's anticipation that competing funds will need to be available to cover the award of the grant should it be approved. Without the impact of this grant, the average of new extramural grants would be $80,000, a decrease of 25 percent from 1990 to 1991.

MEDICAL IMAGE LIBRARY

Mr. Natcher. How much funding are you budgeting for a medical image library in 1991?

Dr. Lindberg. A panel of expert consultants in medical imaging recommended that an image library of an entire male and female human body at millimeter level resolution, including all internal organs and structures, be constructed as a national image resource by the NLM. This "Visible Human" project was estimated by the consultants to optimally require $400,000 in FY 1991, however only $250,000 can be allocated to the project at planned budget levels which will delay the completion of the project. The original schedule for the "Visible Human" included an October 1990 start date and completion of phase I in mid 1992. Now completion is expected in mid 1994.

Mr. Natcher. What would it cost to fully fund the DeBakey group's recommendations regarding medical imaging?

Dr. Lindberg. The Long Range Plan for medical imaging adopted by the NLM's Board of Regents includes not only the acquisition of digital images of body structure, but also analysis and classification of those images so that they can be manipulated by computer

and displayed in three dimensions. The acquisition of the "raw" imaging data will require $1 million. The subsequent processing and analysis of this mass of data by expert anatomists and computer scientists was estimated by NLM's consultant experts to require about 50 staff-years of effort, which would cost approximately $5 million additional. It could be pointed out that Dr. Donald King from the University of Chicago chaired this panel. Dr. DeBakey, Chairman of the Outreach Panel did not participate in this effort.

LITERATURE ACQUISITION

Mr. Natcher. In which areas do assessments indicate that the National Library collection needs improvement?

Dr. Lindberg. Recent collection assessment studies in biotechnology, immunology, dermatology, and health technology assessment have demonstrated that the NLM collection development program has been very successful in identifying and acquiring materials published in the core medical subjects by major commercial sources. Achievement rates for these materials are consistently in the 95-100 percent range. These same studies have also pointed out two areas in which the collection development effort can be enhanced: (1) the collecting of materials in related subjects, e.g., anthropology, psychology, evolution, and (2) the identification and acquisition of technical reports and other items published outside traditional commercial channels, e.g., university departments, national and international associations, and governmental bodies. NLM is developing strategies to improve its collection in these areas.

CATALOGING

Mr. Natcher. What is the average time between the receipt of an item and its cataloging?

Dr. Lindberg. In FY 1989, 83 percent of the medical books published by major U.S. publishers were cataloged and the records released to NLM's online catalog file within 90 days. Cataloging of the great majority of other English language books and about a quarter of the foreign language materials was completed within 3 to 8 months of receipt of the items. The majority of the foreign language items take longer than 8 months to catalog due to the necessity to collect sufficient batches of items in specific languages before contract or interagency agreements can be pursued and the difficulty in hiring staff or locating contractors with expertise in particular languages.

NON-ENGLISH TITLES

Mr. Natcher. How extensive are your non-English holdings?

Dr. Lindberg. At the current time 51.1 percent of the titles in NLM's collection are in English; 48.9 percent are primarily in a foreign language. Approximately 7 percent of the foreign language titles may also include some text in English.

Mr. Natcher. What is your long-range plan for staffing the Biotechnology Center — will 1991 be the end of the buildup in staffing?

Dr. Lindberg. The NCBI currently has approximately 20 employees, with 15 postdoctoral fellows, senior scientists, and support scientists. Because of the unique role of the NCBI, and the strong support by Congress, NIH, and the NLM itself, we have been very successful attracting exceptionally qualified scientists at all levels. This "critical mass" of creativity has enabled us to attain high levels of productivity for a little more than a year since our creation. We would like to reach a steady rate of approximately 30 FTE's in the future.

Mr. Natcher. How much of the Biotechnology Center's activity is information systems research compared to the coordination of databases?

Dr. Lindberg. From its inception, the NCBI has tried to adopt the approach that the administration/coordination of databases cannot be separated from research and development efforts in building those databases. Considerable effort has been devoted to assembling a multidisciplinary staff who have the skills and experience to identify the information needs in biology research as well as the ability to translate those needs into operational systems. Therefore, rather than establishing a separate group solely responsible for database coordination, the NCBI approach has been to involve the development team in the coordination efforts. An example of this process of shared responsibility has been the building of the GenInfo Sequence Backbone database. The design of the database system has involved the input from nearly all of the professional staff and decisions on the scope or the representation of data continue to be based on group meetings. The actual software development work has been performed by a group of approximately four biologists and computer scientists who maintain daily contact with the NLM staff who do the indexing and data input. The indexing staff also has access to research biologists from the NCBI who are assigned to be on-call to clarify biological issues for complicated database entries.

Therefore, to respond specifically to the question, the largest component of the Center's activities is directed to both basic and applied research in molecular biology informatics. Out of this research, methods for representing, analyzing, and retrieving data have emerged which can be applied in operational settings. The amount of effort in database coordination at this time is relatively small, with the most significant portion directed to developing a transition plan for management of the future GenBank contract in September 1992. The NCBI staff have been meeting regularly with the project officers from NIGMS and with the Center for Genome Research to discuss the user requirements for sequence databases and contractual mechanisms for funding these efforts. Database coordination also takes place informally through participation on database advisory committees. Members of the NCBI serve on advisory committees for the Genome Data Bank at

Johns Hopkins, the Department of Agriculture plant genome database activity, and the U.S. Patent Office's biotechnology board (databases of patented sequences).

EXTRAMURAL FUNDING

Mr. Natcher. Provide a breakout of funding among your extramural mechanisms for 1989-1991.

Dr. Lindberg. The breakout of extramural funding for FY 1989-1991 is as follows:

(dollars in thousands)

Extramural Program	FY 1989 Actual	FY 1990 Estimated	FY 1991 Estimated
MLAA			
IAIMS	$2,962	$3,216	$3,345
Resources	$861	$1,829	$1,858
Lib. Info. Sci.	$269	$204	$202
Training & Fel.	$2,636	$3,409	$3,464
Publications	$346	$306	$322
RML Contracts	$2,569	$3,888	$4,000
Total, MLAA	$9,643	$12,852	$13,191
MEDICAL INFORMATICS			
Research	$6,334	$6,636	$6,809
Biotechnology	$4,469	$3,830	$3,991
Total, MI	$10,803	$10,466	$10,800
TOTAL, EXTRAMURAL	$20,446	$23,318	$23,991

INTEGRATED ACADEMIC INFORMATION MANAGEMENT SYSTEMS

Mr. Natcher. Provide a list of the institutions which have received Integrated Academic Information Management Systems grants and the amount which each has received.

Dr. Lindberg. NLM has assisted 14 institutions and organizations in IAIMS Phase I planning (usually 2 years), some for Phase II Model Testing (usually three years), and two for Phase III Implementation (usually for 5 years; NLM has provided support for the first 5 years so far). The awardees in alphabetical order are:

American College of Obstetricians and Gynecologists
Washington, DC
Phase I - $277,853

Baylor College of Medicine
Houston, TX
Phase I, II - $1,015,512

Columbia University
New York, NY
Phase I, II, III - $2,674,124

Dartmouth Medical College
Hanover, NH
Phase I - $88,996

Duke University Medical Center
Durham, NC
Phase II - $1,250,434

Georgetown University School of Medicine
Washington, DC
Phase I, II, III - $2,581,500

Harvard Medical School
Boston, MA
Phase I - $224,742

Johns Hopkins University
Baltimore, MD
Phase I - $95,370

Rhode Island Hospital
Providence, RI
Phase I - $295,528

University of Cincinnati Medical Center
Cincinnati, OH
Phase I, II - $1,358,449

University of Maryland at Baltimore
Baltimore, MD
Phase I, II - $1,096,000

University of Michigan School of Medicine
Ann Arbor, MI
Phase I - $200,000

University of Pittsburgh
Pittsburgh, PA
Phase I - $87,391

University of Utah School of Medicine
Salt Lake City, UT
Phase I, II - $1,050,802

GRATEFUL MED

Mr. Natcher. What is the cost of a GRATEFUL MED software package?

Dr. Lindberg. The cost of a GRATEFUL MED software package is $29.95. The U.S. shipping charge is $3.00.

AIDS

Mr. Natcher. How much have you budgeted for the three new AIDS databases?

Dr. Lindberg. In FY 1991, NLM has budgeted a total of $532,000 for the three AIDS databases.

RESOURCE GRANTS

Mr. Natcher. How many medical library resource grants are awarded each year?

Dr. Lindberg. The number of Medical Library Resource Grants awarded in the past few years has been approximately 15 and, with the new outreach program, will increase to about 25.

GenInfo

Mr. Natcher. How is your GenInfo data bank different from GenBank developed elsewhere?

Dr. Lindberg. The concern over the integration of biological information has been increasing in recent years; with this in mind the GenInfo Backbone Database is the first major database designed from its inception to integrate DNA and protein information. The GenInfo Backbone Database will contain DNA and amino acid sequences and related information from all journals currently indexed by Medline, as well as a selection of additional journals to improve coverage of the plant literature. This information will be available within 1 month of publication, for approximately 90 percent of these articles. GenInfo will only contain those data elements which may be extracted from the literature with a minimal amount of interpretation. As compared to GenBank, the journal coverage is more extensive and the criteria for inclusion less restrictive. For example, shorter stretches of DNA sequence are included, as are amino acid sequences generated in the course of protein engineering. GenInfo, while useful in and of itself, will provide new, more powerful tools for indexing the biological literature, and improve scientists' access to relevant papers. Careful consideration was put into the design of GenInfo to facilitate its use by other database efforts, including explicit definitions of all the fields and the use of standard nomenclature for gene names. PIR (the amino acid sequence database), Kabat's Sequences of Proteins of Immunological Interest, GenBank, and the EMBL Data Library are all planning to evaluate the use of the GenInfo Backbone to facilitate their own projects. Thus the GenInfo Backbone Database is complementary to a number of existing databases, has

its own unique advantages, and will play an important role as a component of the next generation sequence database.

DOCLINE

Mr. Natcher. What is the average response time to DOCLINE document requests?

Dr. Lindberg. We estimate that about 80 percent of the documents requested via DOCLINE are sent out within four days of the receipt of the requests by a participating DOCLINE library. A substantial fraction are sent out within one day of receipt of the request. Depending on the performance of the postal service and other delivery mechanisms, most documents are probably received by requestors 4 to 7 days after the request is made. If the library that fills the request is in the same geographic area as the requestor, the delivery time will be shorter. NLM and many other libraries within the network offer telefacsimile service to fill requests for materials needed for clinical emergencies. Such requests are filled by NLM within 2 hours of receipt.

PRESERVATION

Mr. Natcher. How much 1991 funding is designated for preservation microfilming at other institutions?

Dr. Lindberg. About $235,000 in FY 1991 funding has been designated for preservation of important biomedical literature held by other institutions. This figure includes funding for microfilming and for conservation of original materials.

CURRENT SERVICES

Mr. Conte. In your professional judgment, does the overall budget for the library meet your current service levels?

Dr. Lindberg. In my professional judgment, NLM needs to add $400,000 to meet current service levels. The FY 1991 budget request allows the NLM to begin to address some of the escalating requirements such as increased costs of services provided centrally, literature acquisition, and other basic operating program requirements. However, existing activities will continue at a reduced level. This is particularly true in the extramural grants program.

LIBRARY OPERATIONS BUDGET

Mr. Conte. What kind of cost increases or program increases are facing your library operations budget?

Dr. Lindberg. Expansion in the budget for outreach activities has the expected and desired concomitant effect of increasing the demand for NLM's online and document delivery services. To maintain and enhance the quality of these services in the face of rapidly growing numbers of users and service requests will likely require additional budget and personnel resources in the future.

In addition to the increased demand for its services, NLM continues to face steady inflation in literature prices at the rate of ten or more percent per year. Since NLM buys a substantial number of foreign publications, its literature expenses are subject to additional unpredictable increases due to fluctuations in the currency exchange rates. While recent NLM collection assessment projects have shown that NLM is doing an excellent job in obtaining the majority of publications relevant to biomedicine, they have pointed out deficiencies in the Library's acquisition and bibliographic control of government documents and technical reports. The Library also has a need to gradually expand its indexing coverage of biomedical journals and to enlarge its acquisition and cataloging activities to encompass the increasing numbers of computer-based media on biomedical subjects.

OUTREACH

Mr. Conte. If this committee provided, say $10 million, to your budget, what would be your priority areas for additional funding?

Dr. Lindberg. For the past 10 years, the highest priority of the NLM has been outreach. An additional $10 million would permit NLM to expand ongoing and develop new initiatives to make its services and products better known and more widely used by health care professionals and researchers, particularly in rural and remote areas.

The FY 1991 budget request includes $3.9 million, although the DeBakey Panel Outreach Plan recommends a funding level of $35.5. An

additional $10 million would be utilized to fund the priorities identified by the Panel:

o major enhancements to the Regional Medical Library network as a way of improving NLM's outreach to health professionals with a focus on improving the abilities of the network to support health professionals in underserved areas;

o expansion of Resource Access Grants to provide assistance to small and medium-sized hospitals in gaining to national information sources, especially such institutions in rural and other underserved communities;

o expansion of the Integrated Academic Information Management Systems (IAIMS) program to fund at least one more implementation of an IAIMS model, and to provide planning grants for institutions such as historically black schools that have not, to date, participated in this program;

o increased training opportunities for minority health professionals, especially those participating in underserved areas; an implementation of demonstration programs geared to the improvement of information access in remote locales; and

o augmentation of efforts to publicize and promote the use of NLM's information products and services, especially among minority health professionals, as a means for promoting health and disease prevention.

CORRECTING FALSE INFORMATION

Mr. Conte. Is there anything new in your efforts to correct false or discredited information from your databases?

Dr. Lindberg. NLM continues to alert its users to published retractions and notices of errors in articles previously indexed in NLM databases. In 1989, the Library also began to identify articles that challenge, refute, support, or expand upon another article or letter. These "comments" are linked in the bibliographic reference to the article or articles to which they refer. The Library expects to add several thousand "comments" each year. Notices published by the NIH Office of Scientific Integrity when it has made a determination of misconduct related to NIH funded research will be among the "comments" indexed by NLM in this fashion.

DATABASE SUPPORT

Mr. Conte. I understand that under the auspices of the National Center for Biotechnology Information are the major biomedical databases such as the Protein Identification Resource and GENBANK. How much is included in your budget for these important resources?

Dr. Lindberg. GenBank is currently supported by the NIGMS at a funding level of approximately $5 to $6 million. NLM's contribution in FY 1990 is approximately $60,000 and in past years has ranged up to $350,000. In September 1992, it is planned that this data bank will be administered by NLM's National Center for Biotechnology Information at which time necessary funds will need to be made available.

In FY 1990, PIR will be funded at a level of approximately $998,000 by NLM.

Mr. Conte. In your professional judgment, is it enough?

Dr. Lindberg. It is our professional judgment that the above amounts for FY 1990 will be sufficient to maintain quality operations at GenBank and PIR. It should be noted that in addition to funding support, the NCBI is also making available resources to the databases, primarily in the form of sequence records which will be generated from the GenInfo Sequence Backbone database. By the end of FY 1990, NCBI will be able to furnish sequence information scanned from the journal literature.

FUTURE OF MEDICAL INFORMATION SCIENCES

Mr. Conte. Doctor, your Library stands at the forefront of both information sciences and biomedical advances. What do you foresee as the strategic role of the library in biomedical research over the next 10 years?

Dr. Lindberg. The National Library of Medicine (NLM) is responsible for meeting the information needs of our nation's physicians, research scientists, and other health care professionals as they strive to improve our public health. As a nation, we spend tens of billions of dollars a year on research and treatment of AIDS, cancer, heart disease, and other major human afflictions. Effective biomedical information services are essential to ensure that we maximize the benefits of our enormous investment. The biomedical information programs of the NLM serve as a multiplier, increasing the value of the knowledge resulting from biomedical research. The more rapidly and efficiently health professionals across the country can exploit the latest knowledge gained from research, the faster we will win the fight against AIDS, cancer, and other dreaded human diseases. Guided by the Board of Regents' Long Range Plan, the NLM directs its resources to meeting this information.

In the next 10 years, our strategic role will be to increase our outreach to health professionals, so that they are better able to take advantage of the fruits of biomedical research, and to provide researchers with information tools, such as the products of the National Center for Biotechnology Information, and more advanced capabilities in medical imaging.

Mr. Conte. What contributions can your library make to the information sciences?

Dr. Lindberg. Since its inception, the National Library of Medicine has been at the forefront in the development of new information technologies in the health sciences. From Index Medicus, begun by John Shaw Billings in 1879, the computerized MEDLARS system in 1965 and the first widely available online bibliographic retrieval system, MEDLINE, in 1971, and the early Lister Hill Center experiments in rural areas, to present day developments such as the Unified Medical Language System and evolving information systems in molecular biology and biotechnology, NLM has been a pioneer in information science. Concepts and technologies pioneered by NLM can and have been adapted by others in various fields of endeavor. We will continue to make contributions to the field in areas such as medical vocabulary linkages (the UMLS), biotechnology, the acquisition, storage, retrieval and transmission of images, and high performance computing and gateways.

Mr. Conte. How will you be integrating new technologies to improve medical information and research?

Dr. Lindberg. As new technologies are developed they are evaluated within the context of NLM's mission. The advent of the personal computer and the ability to easily transfer information across telephone lines has made the use of GRATEFUL MED access to NLM's biomedical databases practical for any practitioner. The widespread availability of FAX machines has led to an R&D project investigating the feasibility of automated telefacsimile services. Videodiscs are being developed and tested as innovative methods for teaching medical students and practitioners subjects which are image-intensive. The National Center for Biotechnology is developing new research database and analysis systems which will take advantage of computer networks such as the research Internet and the proposed National Research and Educational gigabit speed network. An underlying theme in all of NLM's research and development is to bring together computers as information engines and networks as information highways to solve the problems which confront researchers, educators and health practitioners.

INTERNATIONAL MEDICAL INFORMATION

Mr. Conte. What have you learned from your foreign colleagues in medical information sciences?

Dr. Lindberg. There is more awareness of the importance of medical information science among international colleagues than ever before. They share U.S. health professionals' view with respect to the importance of medical information science in medical education, and they feel strongly that medical information science should be the answer to international medical education.

In the international scene, one of the most cited applications of medical information science is access to the NLM MEDLINE database, and our international colleagues are very much aware of its

value in their professional practices. Access to MEDLINE overseas is dependant upon the quality and cost of telecommunications in the country. It has been our experience that the growth of access to MEDLINE is less in developing countries where international medical education is needed the most. The availability of MEDLINE on CD-ROM internationally is proving helpful in removing the constraint.

STAFFING NEEDS

Mr. Conte. In your professional judgment, what are your staffing needs for the coming fiscal year?

Dr. Lindberg. In my professional judgment, NLM's staffing needs for the coming fiscal year are 553 FTEs; an increase of 16 FTEs from the budget request. The additional 16 FTEs would provide appropriate staffing levels for special initiatives in outreach, biotechnology, and AIDS, and allow adequate staffing of basic library services.

Mr. Conte. Does this budget provide for that?

Dr. Lindberg. The current budget request includes sufficient resources for 537 FTEs.

INFORMATION TRAINING

Mr. Conte. The DeBakey report said that the NLM should substantially increase the number of Medical Informatics training centers, individual awards for research training and career development, as well as demonstration grants. Do you agree with these recommendations?

Dr. Lindberg. NLM agrees totally with this report. The experience of the institutions with IAIMS support has been that it is extremely difficult to find individuals with the skills necessary to implement such a program. As more institutions are perceiving the potential benefits to be derived from IAIMS concepts, this lack of trained personnel will become even more acute. There are institutions, albeit a very limited number, who could provide a very suitable training environment and experience.

Mr. Conte. Does this budget provide enough to implement these suggestions?

Dr. Lindberg. The projected FY 1991 budget has no funds included to make new institutional training grants nor new funds to award new individual fellowships. While some of the current training grantees could provide such a training experience, they could not begin to meet the demand.

Mr. Conte. If not, how much is necessary?

Dr. Lindberg. In order to meet the demand for individuals to assist in IAIMS activities the DeBakey Report indicates that an additional $7.0 million is needed in FY 1991. With such monies, an institutional program could be mounted as well as the support of

individual fellows. The Outreach report also calls for annual increments to this budget until a total increase of $10 million is reached. The need for these individuals will continue to grow as more institutions start IAIMS projects. One of the reasons there are so few currently is the lack of properly trained personnel.

RHEUMATOLOGY SYSTEM

Mr. Conte. What is the status of the Artificial Intelligence in the Rheumatology program?

Dr. Lindberg. The AI/RHEUM consultant system in rheumatology is one of the world's largest medical artificial intelligence systems for computer-assisted medical diagnosis. It has recently been augmented with a new expert system shell called "CTX", for Criteria Table Expert. The system allows new flexibility in entering, editing and correcting case data (the "shell" is the part of the program which actually performs the reasoning). It analyzes its reasoning on individual cases or on sequences of cases, greatly simplifying the process of managing changes to the knowledge base. CTX works with files created by standard word processors, making it possible for the subject matter expert himself or herself to work directly with the criteria table file to modify a knowledge base.

The system has undergone a preliminary field trial at the University of Utah, and is currently being prepared for formal testing in the clinical setting.

Mr. Conte. Who is benefitting from this system?

Dr. Lindberg. The project objective for AI/RHEUM has been to produce a computer-based rheumatology consultant having performance at the level of an expert rheumatologist. Its intended users are practicing physicians not having specialty training in rheumatology, though the system's use in the education of medical students and house staff is envisioned.

Mr. Conte. Can this system be a model for other medical specialties?

Dr. Lindberg. The system can be a model for other medical expert systems in different medical specialties if the knowledge required for that domain can be represented in the form of criteria tables; criteria tables are listings of findings that are associated with a particular disease. This should be possible in many cases. The important advantage of this representation scheme is that the knowledge base is directly understandable and readily critiqued by subject matter experts in its domain.

COMPUTER AIDED INSTRUCTION

Mr. Conte. There is much promise for computer aided instruction. This field is really starting to take off. With computer assistance, medical students could receive instant feedback on

diagnostic and clinical strategies. Is this an area which you might find of interest?

Dr. Lindberg. Several years ago, NLM established The Learning Center for Interactive Technology (TLC) as the place where health care professionals can learn about new computer and optical disc technologies and their educational applications. At the Center visitors can examine hardware and courseware on their own, observe staff demonstrations of exemplary courseware programs, and confer with staff about courseware design and evaluation. In addition, staff often provide information about applications of interactive technology in different settings, technological trends, and current issues concerning technology development and use.

The goals of The Learning Center are to: 1) monitor current developments in interactive microcomputer and optical disc-based information and education technologies; 2) identify programs that represent unique, state-of-the-art technology applications; 3) develop informative demonstration programs about interactive technology that illustrate prototypical designs and applications; and 4) disseminate information on interactive technology through hands-on experience, technical reports, and informal symposia.

Mr. Conte. Are you involved in research on interactive training programs overall?

Dr. Lindberg. The Educational Technology Branch (ETB) develops prototypes of courseware to demonstrate to the Health Professions Education community various methods for use of computer and optical (analog and digital) disc technology in health professions curricula. ETB also supports field-testing of these new education technologies in a collaborative mode with the test sites furnishing their own hardware and NLM furnishing prototype courseware. Long term goals are: 1) Determining optimum methods for use of computers and visual databases, resident on optical discs, to improve the health professions education process; 2) Developing prototypes of courseware which can be field-tested; 3) Developing and maintaining collaborative relationships with health profession schools under which the schools furnish content expertise for development of prototypes and their own hardware to support student/faculty review and evaluation of courseware.

ARTIFICIAL INTELLIGENCE

Mr. Conte. What artificial intelligence projects are your involved in?

Dr. Lindberg. The Lister Hill National Center for Biomedical Communications (LHNCBC) maintains an Artificial Intelligence Laboratory with many different computer systems as test platforms. Research projects concentrate on the application of artificial intelligence techniques to problems in the representation, retrieval, and manipulation of biomedical knowledge. Staff members are actively involved in research in expert systems, natural language processing, machine learning, and computer-assisted indexing. Professional staff are further involved in

the development of both interactive and more traditional audio-visual exhibits explaining and illustrating these complex research issues and systems for the lay public.

Expert systems are computer programs which combine knowledge of a particular subject area with inferencing mechanisms enabling them to use this knowledge in problem-solving situations. Expert systems can be categorized in two primary types: systems to assist experts in coping with conditions of information overload, and systems for the transfer of expertise. Systems of both types are under active development at the NLM's Lister Hill Center:

1. The AI/RHEUM system is the best known of a series of knowledge-based medical consultant systems using the criteria table form of knowledge representation pioneered by NLM researchers. AI/RHEUM contains information on 32 rheumatologic diseases in its knowledge base. It reasons from 913 patient findings through many hundreds of intermediate hypotheses to these 32 disease conclusions. AI/RHEUM is notable for direct point-and-click mouse access to information from four knowledge sources: text definitions; videodisc images; the disease criteria tables which are the foundation of its medical knowledge base; and GRATEFUL MED for automated dial-out, logon, searching and down-loading from NLM's MEDLARS family of databases without leaving the running rheumatology consultant program.

The AI/RHEUM family of programs also includes several patient management modules which offer therapy recommendations for patients having specific diseases. The most fully developed of these management modules is the one for rheumatoid arthritis.

2. AI/COAG offers diagnostic assistance for problems in human blood clotting. The AI/COAG system performs a differential interpretation of six coagulation laboratory screening tests and offers "Tell Me More" and "Tell Me Reference" information to support its conclusions. A second module acquires and stores a detailed patient blood clotting history. It prints a summary record for the user, then analyzes the history to determine whether the presence of a hemostatic defect makes a further workup desirable. A third AI/COAG module advises emergency room physicians on blood replacement therapy for cases of major trauma.

3. NLM staff is collaborating with nationally known evaluation specialists to develop a general methodology for the evaluation of medical expert systems. The AI/RHEUM diagnostic system is being used as the specific vehicle for the testing of this methodology in the clinical setting in an NIH-funded evaluation program of several years' duration.

4. NLM staff members are also developing a cataloger's assistant system to assist in the NLM cataloging process for new acquisitions, and they are developing the COACH expert searcher system, which will perform some of the functions of an expert medical reference librarian assisting a user in the formulation of queries for MEDLARS searches.

5. The Natural Language Systems Program carries out research

in automated language understanding, with the goal of providing health care professionals with natural and flexible access to biomedical information in computerized form. The major focus of the research group is the development of SPECIALIST, an experimental system for parsing, analyzing and accessing biomedical text. The research involves methods and approaches used in the fields of computer science, information science, and linguistics. The SPECIALIST system runs on the Sun-3 and Sun-4 family of workstations and is implemented in Prolog with some supporting programs implemented in C.

6. A research project in machine learning was initiated in 1989. Machine learning encompasses a wide variety of mechanisms for creating computer programs that improve their performance with use. The objective of this project is to develop and apply methods by which programs can automatically acquire knowledge and put it to work. An early prototype implementation of a knowledge acquisition planner called INVESTIGATOR has been used to explore the molecular evolution of several biological species.

7. The objective of the MedIndEx Project is to develop and test interactive knowledge-based systems for computer-assisted indexing of medical literature currently indexed in the MEDLINE database. By encoding the indexing scheme in a knowledge base and using it to assist indexers, the system is expected to facilitate "expert indexing"; i.e., indexing consistent with published indexing tools upon which indexers currently depend.

8. Members of the LHNCBC staff developed in 1986 and have several times updated an interactive touchscreen videodisc exhibit on "Artificial Intelligence in Medicine". This exhibit opened in January, 1987 at the Museum of Science in Boston as one component of a larger exhibition called "The Age of Intelligent Machines". It has spent 3-month periods there and at such other institutions as the Franklin Institute in Philadelphia, the Fort Worth Museum of Science and Industry in Texas, the California Museum of Science and Industry in Los Angeles, and the Museum of Science and Industry in Chicago. The 3-year national tour closed in late 1989 after the exhibit had been seen by nearly three million visitors. This interactive exhibit has also appeared at four national conferences by invitation and is on permanent display in both the NLM Reading Room and the NIH Visitors' Center.

IAIMS

Mr. Conte. What is the status of the IAIMS program — how is it helping academic medical centers with their information systems?

Dr. Lindberg. Since initiating the IAIMS Grant Program in FY 1984, NLM has supported IAIMS Planning, Model Testing, and/or Implementation Phases at fourteen health science institutions and organizations. During FY 1990, a second competition will be held for IAIMS Phase III Implementation awards; two institutions are expected to receive awards. The result will be four institutions receiving IAIMS Phase III assistance; no other IAIMS grants will

be awarded. Present budgetary constraints do not allow for any other IAIMS awards, either Phase I Planning or Phase II Model Testing, for the foreseeable future.

The IAIMS Program has been successful beyond expectations: the concept of integrated information systems planning and development has been extremely well received by the health sciences community; those IAIMS that have been developed and tested at a few sites with NLM support already show major improvements in knowledge accessibility and utilization; efficiencies in the economics of information and related operations are becoming apparent; the Federal investment in IAIMS activity generates a contribution 10 times as much by the institution and other sources for IAIMS development; and an increasing number of reports, symposia and publications extol the IAIMS Program. There are other important, but unexpected, results becoming apparent; for example, the growing belief in the need of IAIMS in order to undertake successful outcomes assessments of medical care.

FOREIGN LITERATURE

Mr. Conte. Are the costs of foreign medical and research publications continuing to rise?

Dr. Lindberg. Yes. The costs of both domestic and foreign medical and research publications are continuing to rise at rates which exceed the overall inflation rate. For FY 1991, we are projecting an overall increase of about 10 percent if the dollar remains at its current level.

Mr. Conte. Does your FY 1991 request fully account for these price increases?

Dr. Lindberg. Yes. The FY 1991 request for literature is 12 percent over the FY 1990 budgeted figure. Barring unforeseen changes in exchange rates, it allows for projected cost increases plus modest additional amounts for electronic media, technical reports and other literature published outside traditional commercial channels.

PRESERVATION

Mr. Early. What is the present status of NLM's preservation efforts? What is the current target date for completion of this project?

Dr. Lindberg. NLM's preservation program is an ongoing effort which includes: preservation of the NLM collection, a National Plan for preservation of important biomedical literature held by other U.S. institutions and a campaign to increase the amount of new biomedical literature that is published on acid-free paper or other permanent media.

Preservation of NLM's collection involves binding, book repair, staff and user preservation education, disaster prevention, conservation of rare and valuable materials, replacement of missing pages by borrowing items from other libraries, and microfilming of brittle volumes. Since 1986, priority has been given to microfilming of brittle books. By the end of December 1989, 16.5 million pages had been filmed. When the current microfilming contract ends in March 1991, it is estimated that 41 million pages will remain to be filmed. At an average rate of 10,000 volumes per year, filming of the books and serials that are currently brittle should be completed in the year 2000. Future filming efforts will include pamphlets, theses, and the additional books and serials that will have also become brittle by the year 2000. When viable mass-deacidification and paper strengthening facilities become available, NLM will be able to use these technologies to prevent deterioration of the rest of the acidic volumes in its collection.

The National Preservation Plan is an ongoing program which addresses preservation education and information service for librarians throughout the Regional Medical Library Network as well as actual support for the preservation of important and unique items in other library collections.

In FY 1989, NLM funded the first two preservation projects under the National Plan, providing partial support for preservation of unique materials at Yale and UCLA. NLM's 1990 and 1991 budgets include $235,000 for National Plan Projects. The amount of important biomedical literature held by other libraries but not by NLM is difficult to determine because there are significant collections that have not yet been fully organized or cataloged. At a level of $235,000 per year, however, NLM will have to continue to provide some level of support for external preservation projects for many years.

NLM's campaign to encourage publication of the biomedical literature on acid-free paper is meeting with considerable success. The efforts by NLM and other library agencies and groups have heightened awareness of the problems caused by acidic paper, contributed to the development of government and industry specifications and standards for more permanent paper, provided the necessary cost and technical information to publishers, and created improved mechanisms for identifying publications printed on acid-free paper. In the meantime, an increasing number of paper mills are converting to alkaline

papermaking, and supplies of acid-free paper are increasing. The combination of these factors is contributing to a rapid increase in the percentage of new biomedical literature published on acid-free paper. Based on data recently collected by the Library, we estimate that about a third of the titles indexed for MEDLINE and Index Medicus are now printed on acid-free paper. We estimate that virtually all new biomedical journals and books will be printed on acid-free paper by the year 2000.

Mr. Early. How much is included in your FY 1991 request for preservation efforts and will this amount allow you to meet the revised target date for completion of this project?

Dr. Lindberg. A total of $1,900,000 is requested for preservation FY 1991. This amount will enable the Library to identify, prepare, produce and inspect the microfilm, and provide archival film storage for the estimated 10,000 volumes we intend to film in 1991. At this level of funding, it is estimated that the microfilming project of brittle books and serials will be completed by the year 2000. It will also enable NLM to provide necessary preservation and conservation measures for rare materials and other media which require immediate attention and to continue experimentation with electronic storage as a preservation medium. Additional funding for preservation of NLM's own collection will be needed in the future if we are to take advantage of any advances in deacidification or paper strengthening technology.

The FY 1991 request will also allow the Library to allocate $235,000 to partially fund preservation projects in other biomedical libraries. Therefore, progress will continue on the ongoing National Preservation Plan.

CATALOGUING BACKLOG

Mr. Early. What progress has been made in reducing NLM's cataloguing backlog? Is the remaining backlog primarily foreign language books and journals?

Dr. Lindberg. Ten years ago on May 1, 1981, NLM had a backlog of 23,758 books awaiting cataloguing. Currently there are about 7,900 books awaiting cataloguing. Of these 6,000 constitute a six month inventory of English and major foreign language titles. There remains a backlog of about 2,000 items in a variety of foreign languages. In addition there are 1,368 uncataloged serials, half English and half foreign. Of these about 600 constitute a six month inventory. The remainder are English language newsletters, annual reports, etc. and serials in a wide variety of foreign languages.

Mr. Early. What steps need to be taken, and what resources are required, to basically eliminate the cataloguing backlog?

Dr. Lindberg. The majority of items in the existing inventory are foreign language titles cataloged on contract. The major limitation in processing these materials is the lack -

of availability of trained catalogers with the required foreign language expertise. NLM is gradually reducing this backlog as it can identify contractors with the requisite foreign language expertise. The Library of Congress has been helpful in providing cataloging for some of the foreign language books.

MEDICAL LIBRARIAN TRAINING

Mr. Early. Last year, you told us that the NLM planned to convene a panel to review the issue of the training of medical librarians. What is the status of this activity? What recommendations has the panel made?

Dr. Lindberg. The panel to review the training of medical librarians has been deferred at this time. This is a very important matter and I am pleased to report that the Medical Library Association has convened a Knowledge and Skills Task Force. This task force is carefully examining the skills required of the health science librarians of the future, and the educational policies which will assure the maintenance of those abilities throughout their professional career. NLM will examine the recommendations of the task force as part of its planning effort.

IAIMS

Mr. Early. How many IAIMS Phase I, II, and III awards are being funded in FY 1990, and how many of each are proposed to be funded in the FY 1991 budget request?

Dr. Lindberg. The two active IAIMS Phase III Implementation grants have received continuation funding in FY 1990, and two new Phase III grants will be awarded. In FY 1991, continuation funding will be awarded to these four Phase III grants and one Phase II Model Testing grant will be awarded. The Library presently has seven approved, but unfunded applications for IAIMS support in pending status.

ACQUISITION

Mr. Early. How much is included in your budget request for acquisition?

Dr. Lindberg. The 1991 request for literature is $4,251,000, a 12.2% increase over the FY 1990 budgeted figure.

Mr. Early. In your professional judgment, is this a sufficient level of support for this activity or should we be doing more?

Dr. Lindberg. In my judgment this is a sufficient level of support at this time. Barring unforeseen changes in exchange rates, it allows for projected cost increases plus modest additional amounts for electronic media, technical reports and other literature published outside traditional commercial channels.

DEBAKEY OUTREACH PANEL

Mr. Early. To what extent will the NLM be able to implement the recommendations of the DeBakey Outreach Panel in FY 1990?

Dr. Lindberg. NLM is able to fund a number of new Regional Medical Library (RML) Network outreach projects throughout the country and to continue work that was underway in the Pacific Northwest (Alaska, Idaho, Montana, Washington and Oregon) and the states of West Virginia and Mississippi. All of these projects target underserved health professionals. In the West Virginia CONSULT project, hospital librarians have been conducting GRATEFUL MED training throughout the state. At this time, more than 200 health professionals have attended one of these sessions, resulting in distribution of 147 GRATEFUL MED software packages and 130 MEDLARS codes. In the Pacific Northwest, an RML staff member has demonstrated GRATEFUL MED to more than 260 hospital administrators and medical staff in 40 sites--and 70% of these individuals have since become users of the information services. New projects include the state of Massachusetts, the Bronx in New York City, and rural areas of Western Maryland, New York State, and Southern Iowa. Three additional projects, in Oklahoma and North and South Dakota target health professionals in the Indian Health Service. In addition to the RML projects, NLM is providing individual hospital libraries with the opportunity to receive funds via Competitive Purchase Orders to conduct local outreach programs. The primary purpose is to expand the service areas of these libraries to include health professionals who do not have access to a medical library. The methodology features introduction of GRATEFUL MED so that the health professional can identify the needed information and then obtain the documents through the Regional Medical Library Network. Up to 20 projects will be funded.

The DeBakey Outreach Panel also recommends expanding NLM's extramural resource grant program of "Access" grants, increasing funding for the IAIMS Program, and increasing the number of Medical Informatics training centers, individual awards for research training and career development, and demonstration grants. Current budgetary constraints will not permit any new IAIMS Phase I Planning or Phase II Model Testing awards, only two new Phase III Implementation awards, no new institutional research training grants, and only a few new resource "Access" awards in FY 1990.

OUTREACH

Mr. Early. How much is included in your FY 91 request to carry out the DeBakey panel recommendations?

Dr. Lindberg. The fiscal year 1991 budget request includes $3.9 million for outreach, an increase of 2.6 percent from the fiscal year 1990 level.

Mr. Early. How does your budget request differ from the panel's recommendations?

Dr. Lindberg. The panel's Outreach report called for a $35.5 million funding level for outreach activities in fiscal year 1991. The $3.9 million requested will allow extremely modest enhancements in the RML network and Resource Access as well as very nominal increases for Training Grants and publicity and new products and services. The $35.5 million recommended by the Outreach report would provide sufficient funding for necessary enhancements for these programs and resources to support an increased number of institutional models through the IAIMS program.

ELECTRONIC IMAGING

Mr. Early. What are the NLM's plans in the area of electronic imaging techniques?

Dr. Lindberg. NLM's electronic imaging activities are included as subsets of ongoing research and development in areas of image communications and medical informatics. By applying state-of-the-art techniques, which include image processing, image encoding and computer modeling, NLM plans to upgrade its future information databases to include medical images. NLM is presently pursuing two major programs which use electronic imaging techniques.

First is the "Visible Human" project which was recommended by a panel of national expert consultants in medical imaging. Goals of this project include the construction of a computer-based medical atlas of human anatomy at millimeter level resolution, which will enable the reconstruction of three-dimensional images of all body structures.

A second program for electronic imaging is focused on the electronic presentation and archiving of the NLM's biomedical literature collection. Research is being conducted in NLM's Lister Hill Center laboratories on techniques for converting paper documents to digital images. This technology will not only preserve the information content of the literature, but also restore deteriorated originals to high quality through enhancement techniques.

CURRENT SERVICES

Mr. Early. Does the budget adequately cover NLM's current services needs?

Dr. Lindberg. NLM requires an additional $400,000 to meet current services needs. The FY 1991 budget request allows the NLM

to begin to address some of the escalating requirements such as increased costs of services provided centrally, literature acquisition and other basic operating program requirements.

Mr. Early. If not, what services or programs will be curtailed?

Dr. Lindberg. Existing activities will continue at a reduced level. This is particularly true in the extramural grants program.

BUDGET NEEDS

Mr. Early. What was the NLM's original budget request and how does it differ from the request before us?

Dr. Lindberg. NLM's FY 1991 budget request to NIH was $164,626,000. The request to NIH included funds to support the Outreach effort at the level recommended by the DeBakey report and funds necessary to implement a number of activities recommended in the NLM Board of Regent's Long Range Plan. Those activities included 1) expanding the programs conducted by the National Center for Biotechnology Information, 2) improving progress in the development of a Unified Medical Language System, and 3) increasing efforts in the development of electronic imaging and computer-based educational resources. The request to NIH also included a greater level of resources devoted to enhancing AIDS information.

PRIORITIES

Mr. Early. If an increase were provided over the FY 91 budget request, how would you use these additional funds?

Dr. Lindberg. In my professional judgement, the top priority is to implement the DeBakey Panel Outreach Plan. Therefore, NLM would use an increase over the 1991 budget request to fund the priorities identified by the Panel:

- o strengthen the Regional Medical Library network;
- o fund additional resource "access" grants to community-based health institutions including small hospital libraries;
- o award additional Integrated Academic Information Management System grants; and
- o expand intramural efforts to improve NLM products and services.

These actions are all aimed at improving access to and awareness of NLM's information products and services. Outreach and improved access are but two sides of the same coin.

Mr. Early. What would your priorities be?

Dr. Lindberg. In making every effort to support full implementation of the plan, NLM would strive to fund the following priorities.

- Strengthen the highly successful Regional Medical Library Network and forge a new relationship between its 3,000 member institutions and the National Library of Medicine. Library sources within the Network should continue to be improved and staffs of member institutions should be trained to use NLM's databases and other electronic information systems, and to increase the use of these database resources among users. The Network should act as a "field force" in bringing NLM's products and services to the individual health professional.

- Expand NLM's program of direct "access" grants to community-based health institutions to enable them to connect electronically to national information sources. Similarly, NLM should widen its support of IAIMS--an ambitious program to integrate and manage the wide variety of computerized medical information sources found in large academic medical institutions.

- Expand grant support for training, fellowships, and project demonstrations. These programs aim to supply the critical need for community-based health professionals who are skilled in the use of modern information systems.

- Investigate the information seeking habits of American health professionals, determine how best to increase their awareness of NLM information services, and put in place a permanent "feedback" mechanism to learn from users how these services can be improved. The resulting information can be used by the NLM to expand its own research and development program to improve information services.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

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National Library of Medicine

For carrying out section 301 and title IV of the Public Health Service Act with respect to health information communications [$83,311,000] $89,916,000.

(Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 1990.)

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Amounts Available for Obligation 1/

	1989 Actual	1990 Appropriation	1991 Estimate
Appropriation	$74,626,000	$83,311,000	$89,916,000
Enacted administrative reduction	-895,000	-379,000	---
Sequestered order	---	-1,071,000	---
Subtotal, adjusted appropriation	73,731,000	81,861,000	89,916,000
Comparative transfers to:			
DRR for administrative costs of RCMI program	-2,000	---	---
Fogarty International Center	-8,000	-8,000	---
Comparative transfers from:			
Office of the Director, NIH for cost increase in FTEs	+547,000	---	---
NIH, DRR for Biomedical Research Technology Grant Assistance	+3,615,000	+3,875,000	---
Subtotal, adjusted budget authority	77,883,000	85,728,000	89,916,000
Unobligated balance lapsing	-339,000	---	---
Total obligations	77,544,000	85,728,000	89,916,000

1/ Excludes the following amounts for reimbursable activities carried out under this account: 1989: $6,154,000; 1990: $7,645,000; 1991: $8,396,000.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine
Budget Mechanism
(Dollars in thousands)

	1989 Actual		1990 Appropriation		1991 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Extramural Programs:						
Grants:						
Noncompeting	54	$12,413	56	$13,608	75	$16,234
Competing	41	5,466	55	5,822	23	3,757
Subtotal, Grants	95	17,879	111	19,430	98	19,991
Contracts:						
Noncompeting	7	2,569	7	3,888	7	4,000
Competing	--	---	--	---	--	---
Subtotal, Contracts	7	2,569	7	3,888	7	4,000
Total, Extramural	102	20,448	118	23,318	105	23,991
	FTEs		FTEs		FTEs	
Intramural Programs:						
Library Operations	310	31,981	312	34,469	315	36,552
Lister Hill Center	66	10,276	73	11,199	73	11,734
Biotechnology Center	12	4,764	14	5,723	24	5,989
Toxicology Information	35	4,116	35	4,420	35	4,647
Total, Intramural	423	51,137	434	55,811	447	58,922
Research Management and Support	88	6,298	90	6,599	90	7,003
Total Budget Authority	511	77,883	524	85,728	537	89,916
HIV/AIDS	(2)	(79)	(7)	(493)	(8)	(532)

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

CROSSWALK - 1989 Actual

Program Activity	Mechanism				
	Extramural Programs		Intramural Programs	Research Mgmt. and Support	Total
	Grants	Contracts			
Extramural Programs					
Medical Library Assistance	$7,075,000	$2,569,000	---	---	$9,644,000
Medical Informatics	10,804,000	---	---	---	10,804,000
Total, Extramural	17,879,000	2,569,000	---	---	20,448,000
Intramural Programs					
Library Operations	---	---	$31,981,000	---	31,981,000
Lister Hill Center	---	---	10,276,000	---	10,276,000
Biotechnology Center	---	---	4,764,000	---	4,764,000
Toxicology Information	---	---	4,116,000	---	4,116,000
Total, Intramural	---	---	51,137,000	---	51,137,000
Research Management and Support	---	---	---	$6,298,000	6,298,000
Total Budget Authority	17,879,000	2,569,000	51,137,000	6,298,000	77,883,000

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

CROSSWALK - 1990 Appropriation

Program Activity	Mechanism				
	Extramural Programs		Intramural Programs	Research Mgmt. and Support	Total
	Grants	Contracts			
Extramural Programs					
Medical Library Assistance	$8,964,000	$3,888,000	---	---	$12,852,000
Medical Informatics	10,466,000	---	---	---	10,466,000
Total, Extramural	19,430,000	3,888,000	---	---	23,318,000
Intramural Programs					
Library Operations	---	---	$34,469,000	---	34,469,000
Lister Hill Center	---	---	11,199,000	---	11,199,000
Biotechnology Center	---	---	5,723,000	---	5,723,000
Toxicology Information	---	---	4,420,000	---	4,420,000
Total, Intramural	---	---	55,811,000	---	55,811,000
Research Management and Support	---	---	---	$6,599,000	6,599,000
Total	19,430,000	3,888,000	55,811,000	6,599,000	85,728,000

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

CROSSWALK - 1991 Estimate

Program Activity	Mechanism				
	Extramural Programs		Intramural Programs	Research Mgmt. and Support	Total
	Grants	Contracts			
Extramural Programs					
Medical Library Assistance	$9,191,000	$4,000,000	---	---	$13,191,000
Medical Informatics	10,800,000	---	---	---	10,800,000
Total, Extramural	19,991,000	4,000,000	---	---	23,991,000
Intramural Programs					
Library Operations	---	---	$36,552,000	---	36,552,000
Lister Hill Center	---	---	11,734,000	---	11,734,000
Biotechnology Center	---	---	5,989,000	---	5,989,000
Toxicology Information	---	---	4,647,000	---	4,647,000
Total, Intramural	---	---	58,922,000	---	58,922,000
Research Management and Support	---	---	---	$7,003,000	7,003,000
Total	19,991,000	4,000,000	58,922,000	7,003,000	89,916,000

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NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Summary of Changes

1990 Estimated budget authority	$85,728,000
1991 Estimated budget authority	89,916,000
Net Change	+4,188,000

Changes:	1990 Current Estimate Base Pos. (FTEs)	1990 Current Estimate Base Budget Authority	Change from Base Pos. (FTEs)	Change from Base Budget Authority
A. Built-in:				
1. Pay Raise		$23,700,000		+$831,000
2. Within-grade increases		23,700,000		+316,000
3. Annualization of January 1990 pay raise		23,700,000		+230,000
4. One extra day of pay		23,700,000		+93,000
5. Federal Employees Compensation Fund		120,000		+4,000
6. Unemployment compensation increase		64,000		+2,000
7. FTS rate increase		236,000		+8,000
8. Payment for centrally furnished services		8,241,000		+471,000
9. Increased cost of supplies, materials, literature and other expenses		30,469,000		+1,592,000
10. DHHS Working Capital Fund		163,000		-8,000
Subtotal				+3,539,000
B. Program:	No.	Amount	No.	Amount
1. Grants:				
a. Noncompeting	56	13,608,000	+19	+2,626,000
b. Competing	55	5,822,000	-32	-2,065,000
Total	111	19,430,000	-13	+561,000
2. Contracts:				
a. Noncompeting	7	3,888,000	--	+112,000
3. Intramural Programs	Pos. (FTEs) 434	55,811,000	Pos. (FTEs) +13	-24,000
Subtotal				+649,000
Total changes				+4,188,000

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Budget authority by activity
(Dollars in thousands)

	1989 Actual		1990 Appropriation		1991 Estimate	
	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Programs						
Med'l Library Assistance		$9,644		$12,852		$13,191
Medical Informatics		10,804		10,466		10,800
Total, Extramural		20,448		23,318		23,991
Intramural Programs						
Library Operations	310	31,981	312	34,469	315	36,552
Lister Hill Center	66	10,276	73	11,199	73	11,734
Biotechnology Center	12	4,764	14	5,723	24	5,989
Toxicology Information	35	4,116	35	4,420	35	4,647
Total, Intramural	423	51,137	434	55,811	447	58,922
Research Management and Support	88	6,298	90	6,599	90	7,003
Total Budget Authority	511	77,883	524	85,728	537	89,916

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National Library of Medicine

Budget Authority by Object

	1990 Appropriation	1991 Estimate	Increase or Decrease
Total number of full-time permanent positions	504	517	+13
Total compensable workyears:			
Full-time equivalent employment	556	569	+13
Full-time equivalent of overtime and holiday hours	10	10	---
Average ES salary	$76,500	$90,270	+13,770
Average GM/GS grade	10.0	10.0	---
Average GM/GS salary	$31,623	$32,453	+830
Average salary, grades est. by act of July 1, 1944 (42 U.S.C. 207)	$58,525	$60,061	+1,536
Average salary of ungraded positions	$16,788	$16,788	---
Personnel compensation:			
Permanent positions	18,388,000	19,268,000	+880,000
Positions other than permanent	1,964,000	2,023,000	+59,000
Other personnel compensation	357,000	368,000	+11,000
Special personal services payments	20,000	21,000	+1,000
Subtotal, personnel compensation	20,729,000	21,680,000	+951,000
Personnel benefits	2,971,000	3,084,000	+113,000
Benefits for former personnel	22,000	23,000	+1,000
Travel and transportation of persons	496,000	498,000	+2,000
Transportation of things	153,000	153,000	---
Rent, communications and utilities	1,419,000	1,454,000	+35,000
Printing and reproduction	1,473,000	1,498,000	+25,000

	1990 Appropriation	1991 Estimate	Increase or Decrease
Other services:			
Project contracts	$14,979,000	$15,503,000	+$524,000
Centrally furnished services	8,241,000	8,604,000	+363,000
Other	7,360,000	8,420,000	+1,060,000
Supplies and materials	613,000	617,000	+4,000
Equipment	4,172,000	4,134,000	-38,000
Literature	3,670,000	4,257,000	+587,000
Grants, subsidies & contributions	19,430,000	19,991,000	+561,000
Total budget authority by object	85,728,000	89,916,000	+4,188,000

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National Library of Medicine

Significant Items in House Appropriations Committee Report

Item FY 1990 House Report	Action Taken or to be Taken
1. The NLM's statutory responsibility was revised to include authority to publicize the availability of its products and services. In response to this directive, the Library's Board of Regents established an Outreach Planning Panel to advise the NLM in this area. The Committee intends that a significant portion of its increase for the Library be allocated to expanding these outreach programs. (p. 86)	1. The increase will be utilized by the NLM to expand its outreach programs in publicizing the availability of its products and services. The NLM will enhance the Regional Medical Library network, expand "Access" grants to hospitals, strengthen research training and fellowships, and promote awareness of the products and services of the NLM.
2. The Committee is concerned that the Historically Black Colleges and Universities have not participated fully in the services of the National Library of Medicine. The Committee urges NLM to work closely with HBCU's and encourage applications from these institutions. (p. 86)	2. NLM has taken several initiatives to better serve minorities in historically black medical colleges. Efforts to insure full and equal access for minority institutions and individual investigators have been emphasized. Presentations of NLM's programs and services have been made to officials of several minority institutions including historically black colleges. Visits and planning meetings with black medical colleges will continue.

National Library of Medicine

Significant Items in Senate Appropriations Committee Report

Item FY 1990 Senate Report	Action Taken or to be Taken
1. The National Library of Medicine maintains a computerized data base and bibliography of medical research knowledge and recent findings. The Committee has been concerned that an inadequate number of health professionals and health institutions have taken advantage of this system. In order to expand the usefulness of this system, particularly to rural areas, the Committee has directed the National Library of Medicine to strengthen its regional medical library network in order to expand direct access to community based health institutions and doctors. (p. 38)	1. The regional medical library (RML) network has developed specific outreach services to health professionals in underserved areas; promoted resource sharing among health sciences libraries, encouraged and supported use of online services through NLM online system updates, demonstrations of NLM databases, and online training for health professionals; and provided training and consultation to hospital librarians to improve information service to health professionals. In FY 1991, one-third of the funds earmarked for outreach efforts will be utilized to support RML enhancement projects to provide "access to community-based health institutions and doctors."
2. The Committee is pleased that at its direction the NLM is developing an active outreach program to make its services and products better known and more widely used by health care professionals and researchers, particularly in rural and remote areas. The Committee is disappointed, however, that all the recommendations made by the panel require additional funding totaling $26,000,000 or a 33 percent increase in the budget of the National Library of Medicine. The Committee strongly believes that all the existing NLM mechanisms need to be examined to see how this objective can be met. The Committee requests a report before February 1990 on how	2. NLM is in the process of preparing this report and expects it to be available shortly.

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Item FY 1990 Senate Report	Action Taken or to be Taken
this objective can be met within existing resources. (p. 163)	
3. The Committee supports the continued establishment of the National Center for Biotechnology Information. (p. 163)	3. Increased funding and manpower continue to be made available to the Center. These resources are strengthening a number of ongoing NLM projects and providing support for new programs in the dissemination of biotechnology information. The NCBI has created an NIH intramural research program and assembled a multi-disciplinary research group with backgrounds in molecular biology, genetics, biochemistry, computer science, and mathematics to conduct basic and applied research in computational biology.
4. The Committee is very pleased with the continuing efforts of the National Library of Medicine to systematically incorporate and expand the scope of nursing reference materials and resources in its facilities. The NLM is urged to continue its efforts to collaborate with, and to involve, professional nurses in the planning, development, and evaluation of its programs. (p. 164)	4. NLM continues to involve professional nurses in both its chartered and ad hoc advisory committees. Additionally, NLM participates in the Interagency Counsel for Library Resources in Nursing to provide information on NLM's current services and receive feedback on useful enhancements. NLM has provided its technical expertise in vocabulary development and information to groups convened by the National Center for Nursing Research. In addition to these activities, NLM continues to acquire and catalog the world's nursing literature and to collaborate with the American Journal of Nursing Company to index nursing journals for MEDLINE and to produce the International Nursing Index.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1990 Amount Authorized	1990 Appropriation	1991 Amount Authorized	1991 Budget Estimate
Research and Investigation..... Section 301	Title III, Part A	42§241	Indefinite	$72,876,000	Indefinite	$76,725,000
National Library of Medicine.....	Title IV, Part D Section 465-467	42§286	Indefinite		Indefinite	
Medical Library Assistance.....	Title IV, Part D Section 469-477	42§286b	Such sums as necessary	12,852,000	Authorizing legislation to be requested	13,191,000
Total Budget Authority..				85,728,000		89,916,000

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National Library of Medicine

Appropriations History

Year	Estimate To Congress	House Allowance	Senate Allowance	Appropriation 1/
1980	$42,088,000	$42,431,000	$44,000,000	$43,979,000
1981	45,188,000	44,730,000	44,569,000	44,666,000
1982	41,956,000 2/	46,252,000	46,677,000	45,035,000
1983	46,043,000	46,043,000	51,943,000	51,943,000
1984	49,616,000	42,263,000 3/	41,963,000 3/	49,613,000
1985	51,320,000	43,820,000 3/	53,500,000 4/	55,910,000
1986	53,320,000	46,972,000 3/	60,000,000	57,808,000
1986 Sequester				-2,486,000
1987	56,408,000	61,588,000	62,088,000	61,838,000
1988	64,399,000	71,465,000	70,399,000	67,910,000
1989	70,626,000	64,836,000 3/	70,626,000	73,731,000
1990	78,729,000	83,311,000	80,729,000	82,932,000 5/
1990 Sequester				-1,071,000
1991	89,916,000			

1/ Reflects enacted supplementals, rescissions and reappropriations.
2/ Reflects the September amendment; the original request was $47,677,000.
3/ Excludes funds for Medical Library Assistance Act programs not considered.
4/ Includes $7,500,000 for Medical Library Assistance Act programs under the Continuing Resolution. Does not include $607,000 transfer of unobligated balances from the Health Resources and Services Administration.
5/ Excludes enacted administrative reduction of $379,000.

Justification

National Library of Medicine

	1990 Appropriation		1991 Estimate		Increase or Decrease	
	FTE	BA	FTE	BA	FTE	BA
TOTAL.....	524	$85,728,000	537	$89,916,000	+13	+$4,188,000
HIV/AIDS..	(7)	(493,000)	(8)	(532,000)	(+1)	(+39,000)

General Statement

The services of the National Library of Medicine, and the unparalleled collections on which they are based, are essential to both biomedical research and the delivery of health care in this country. As a result of the pioneering work of the Library in computer-based bibliographic systems, information is available when and where it is required and in a form that can be readily used. In addition to its collections and services, the Library conducts research of the highest quality into knowledge-based medical consulting expert systems, electronic biomedical imaging technology, and electronic information storage and retrieval.

The Library's programs are conducted and supported through the following NLM budget activities: (1) extramural programs, (2) intramural programs, and (3) research management and support. The primary goals of these activities are to make the ever-increasing body of biomedical knowledge available to scientists and health professionals, facilitate and expedite advances in biomedical research, and enhance medical education and practice. Ultimately, the public's health and quality of life can be enhanced by these activities.

Under the Medical Library Assistance Act the NLM's extramural programs fund several grant and contract activities of importance to the biomedical community. Two areas of emphasis in the last few years have been the development of Integrated Academic Information Management Systems (IAIMS) and the Medical Informatics program, including support for biotechnology research grants. Also within the extramural program, support is provided for the U.S. Regional Medical Library Network. The goals of this Network are to improve access to and delivery of information to health professionals; to develop and maintain an effective and efficient network of health sciences libraries; and to develop and maintain links between the Network and other information systems or health professional organizations. Support take the form of contracts to the seven Regional Medical Libraries themselves and resource grants to institutional members of the Network.

The NLM's intramural program includes four major components: Library Operations, Lister Hill National Center for Biomedical Communications, the National Center for Biotechnology Information, and the Toxicology Information Program.

Library Operations (LO), as the center for all collection-based operations, is the Library's largest component. LO acquires and preserves the world's biomedical literature; organizes this literature by cataloging and indexing; disseminates indexing and cataloging data in publications, online files, and other machine-readable forms; lends or copies documents in the NLM collection as a backup to document delivery service provided by other U.S. biomedical libraries; and provides reference and research assistance to health professionals. NLM's immense computerized system, MEDLARS, is indispensable in carrying out all of these operations.

The Lister Hill National Center for Biomedical Communications is the research and development arm of NLM. Within its broad mandate, the experts in the Lister Hill Center apply the latest in computer and communications technology to developing better systems for handling health information and health sciences education. The Unified Medical Language System, knowledge-based medical expert consulting systems, electronic information storage and retrieval, and electronic biomedical imaging technology are the areas of emphasis as we enter the Nineties.

The National Center for Biotechnology Information (NCBI), mandated by legislation in late 1988 and established as an NLM component in 1989, is the Nation's focal point where the sciences concerned with molecular biology and computer science merge for the advancement of biomedical knowledge. The NCBI's resources are directed towards creating automated molecular biology information systems, doing research in the development of advanced methods of information of computer-based information processing in biotechnology, facilitating the use of biotechnology-related databases, and coordinating efforts to gather biotechnology information worldwide.

NLM's Toxicology Information Program (TIP) develops and maintains specialized online databases on drugs and chemicals toxic to man. TIP operates a publicly accessible system of online data files called TOXNET and prepares and publishes bibliographies and reports. The TIP collaborates extensively with other government and nongovernment agencies and organizations in developing its computer-based services.

Support activities are responsible for the overall scientific direction and administrative management necessary for the effective and efficient operation of all NLM activities, including extramural grant and contract programs.

The NLM collections currently number almost 5 million items--books, journals, technical reports, manuscripts, microfilms, pictures, audiovisual materials, and computer software. This enormous resource, the world's largest, reflects the biomedical and related sciences from all periods and all corners of the globe. Mere collection is not sufficient, however, for this mass would

be of limited value if it were not for NLM's functions of indexing, cataloging, announcing, and distributing these data.

Finally, the Library is placing increasing emphasis on outreach--activities that will ensure the optimum use of these resources by all varieties of health professional, including those in medically underserved areas of the country.

Overall Budget Policy

The FY 1991 budget request for the National Library of Medicine is $89,916,000, an increase of 4.9 percent over the FY 1990 estimate. The request includes support for 537 full-time equivalent (FTEs). The request continues to emphasize support for library operations including literature acquisition, management and preservation, and for grants in Integrated Academic Information Management Systems (IAIMS), training, medical informatics, biotechnology and other high priority research and development initiatives. The request also includes the continuation of funding for outreach efforts initiated in FY 1990. Overall, NLM programs will be maintained at approximately the current level.

The request includes $3,911,000 for Outreach activities; an increase of $98,000 from the FY 1990 estimate of $3,813,000. At this level NLM will continue its efforts to build and increase existing outreach activities. The NLM will enhance the Regional Medical Libraries network, expand "Access" grants to hospitals, strengthen research training and fellowships, and promote awareness of the products and services of the Library.

For extramural programs, the FY 1991 request is $23,991,000, a $673,000 or 2.9 percent increase over the FY 1990 estimate. The request will support a total of 105 awards. For biotechnology information activities, this request includes support for 16 noncompeting and no competing grants, the same number as the FY 1990 estimate. For IAIMS, this includes funding for four non-competing Phase-III awards. No Phase-I and one Phase-II award will be made in FY 1991.

With regard to intramural programs, and research management and support activities, $3,111,000 and $404,000 increases are provided respectively. These increases will help to cover rising costs, including those for services provided centrally. For example, management fund charges increase from $8,241,000 in the FY 1990 current estimate to $8,712,000 in FY 1991. Other increases covered by the FY 1991 request are pay raise, FTS, and other built-in increases for personnel and basic operating program requirements. Also included is $587,000 for literature acquisition costs.

Funding for the National Center for Biotechnology Information is $5,989,000 at the FY 1991 request level, compared to $5,723,000 in FY 1990, a 4.6 percent increase. These resources would support the continuation of projects that are key to the development of improved and enhanced biotechnology information services.

Program Accomplishments

NLM Long Range Plan Update

In January 1987, NLM's Board of Regents published a Long Range Plan to guide the Library in using its human, physical, and financial resources to fulfill its mission. The Long Range Plan emphasizes the present urgent need for improved access by health care professionals and scientists to the fast growing literature of newly discovered biomedical concepts, treatments, and preventatives--across a wide range of practical and theoretical problems. NLM is following the recommendations of the Plan quite carefully in the management of the Library and the implementation of new activities.

In 1988, the Board undertook to update the plan focusing on newly emergent areas and a re-visiting some topics not completely specified in the original Plan. Areas currently identified are outreach, electronic imaging, and the training of medical librarians. Under the direction of the Board, NLM convened working groups of consultants to develop more detailed plans in these areas.

NLM's current outreach program is built upon a basic infrastructure consisting of the Regional Medical Library (RML) network, Medical Library Assistance Act Resource Access Grants, Integrated Academic Information Management Systems (IAIMS) grants, Training Grants in medical informatics, and ongoing research and development leading to new and enhanced products and services.

A Planning Panel on NLM's Outreach Programs, chaired by Dr. Michael DeBakey, issued a report in 1989 that has been incorporated by the Board of Regents into the NLM Long Range Plan, recommending that NLM build upon and enhance existing outreach activities to increase their impact on the health science community. Underlying the DeBakey report recommendations is the belief that access to NLM's MEDLINE database, as well as other NLM products and services, can, to a significant extent, compensate for the relatively poor status of traditional channels of health-related communication in rural and other professionally isolated communities populated by minority and other low-income groups. Working in collaboration with the member libraries of the Regional Medical Library Network, including health science libraries at historically black schools, and with other governmental and community-based organizations, demonstrations testing alternative strategies for improving information access will be put in place.

In the area of electronic imaging, the Plan encouraged NLM to consider building and disseminating medical image libraries much in the same way it acquires, indexes, and provides access to the biomedical literature. A Planning Panel was convened to define a proper role for NLM in electronic imaging. The Panel was chaired by Dr. Donald West King of the University of Chicago and represented both the producers and potential users of computer-based biomedical images in research, medical education and patient care.

The Panel found that the new computer-based technologies are providing an unprecedented opportunity to supplement the traditional images of medicine. They recommended that NLM proceed with the initial phases of a project to develop an image data set of an entire human male and female, and later should support follow-on research efforts to develop applications which can extract, manipulate, and display image subsets on the basis of organs, tissues, body systems and biologic function. The next step would be to expand upon initial image libraries composed of normal structures to specialized image collections which represent related functions, such as embryological development, normal and abnormal variations, and disease-related images, and also to encourage and support investigator-initiated research in imaging techniques.

Biotechnology

The National Center for Biotechnology Information (NCBI) was founded to provide enhanced information services to assist researchers in accessing and using the ever-increasing volume of data in the area of molecular biology. Within the past year a multi-disciplinary research group of computer scientists, molecular biologists, biochemists, and structural biologists has been assembled to investigate fundamental problems in gene organization and protein structure and to develop new models and algorithms for sequence analysis.

The Center has begun the development of a database building system that addresses the problems of integrated information as well as timeliness and accessibility. Building upon the NLM's long experience with managing biomedical databases, informatics specialists within NLM identify and index new DNA and protein sequences, creating new sequence records from the 3500 journals that are regularly scanned for the MEDLINE database. The goal of this database, called GenInfo, is to provide a core of biological information about sequences, including the sequence itself, that will be available to researchers within a month of publication. Within the design of the database are mechanisms that will link GenInfo to more detailed information in other sequence and protein structure databases, as well as to the bibliographic database, MEDLINE.

Efforts have been directed to developing a "software toolkit" to ease information access. The "toolkit" is a set of computer programs that is modular, easily adaptable to other systems, useful in the near term on present machines but also flexible enough to accommodate future advances in software engineering and hardware design. The first major application has been completed and consists of a program to construct computerized maps that integrate DNA sequences, restriction site and genetic linkage information. Other tools under development include advanced methods for finding sequence similarities in database searching and evaluating their statistical significance, simultaneous multiple sequence alignment and sequence motif construction and pattern matching.

To ensure information access, the Center fosters scientific communication in the area of computers as applied to molecular biology and genetics by sponsoring meetings, workshops, and lecture series. For example, a major

international symposium, "Macromolecules, Genes, and Computers", attended by over 300 computer scientists and biologists was convened under NCBI auspices in August. A Biotechnology Lecture Series at the NLM has brought eminent biologists to address key issues in molecular biology and genetics. Hands-on computer workshops for training NIH scientists in the use of analytic software have been conducted in the NLM PC training facility.

Another component of outreach to the scientific community is the support of grants and postdoctoral training in computational molecular biology. In FY 1989, 14 grant awards were awarded in the areas relating to biotechnology.

Integrated Academic Information Management Systems

NLM provides grant assistance to medical centers, health science institutions, and organizations for planning and development projects leading to the implementation of Integrated Academic Information Management Systems (IAIMS). IAIMS are institution-wide computer networks that link and related library systems with individual and institutional databases and information files, within and external to the institutions, for patient care, research, education, and administration. Interest in NLM's IAIMS Program is extensive, reflecting recognition of the critical need to provide better access to the scholarly record and the vast array of medical databases. IAIMS grants have provided support to a total of 14 institutions for planning (Phase I) and/or development (Phase II) of institution-wide systems. In FY 1989, two awards were made for Phase III, full implementation of prototypes of these integrated systems.

Library Operations

NLM's primary responsibility is to provide easy intellectual and physical access to the world's biomedical literature for health professionals and researchers - irrespective of their geographic locations. In FY 1989, Library Operations took several steps to improve NLM's basic services and to make them more accessible to their intended users.

The NLM recently completed a study that seeks to answer the question: "Does MEDLINE make a difference?" The question is of fundamental concern to NLM and medical libraries throughout the world. The study was carried out using the Critical Incident Technique (CIT); a systematic approach to obtaining and analyzing reports of behavior leading to successful or unsuccessful outcomes on a task or process, and, in all, the study generated detailed accounts of more than 1100 MEDLINE searches.

The results provide detailed insight into the impact of MEDLINE information on the decisions and actions of health professionals, and fills the long-felt need to document the practical value of MEDLINE for the biomedical community. The study reveals a remarkable diversity in the uses to which MEDLINE is put, and should be useful in such areas as online training, GRATEFUL MED development, and especially for outreach to new user communities.

As part of NLM's efforts to improve access, substantial enhancements were made to GRATEFUL MED, a micro computer search package which allows users to search MEDLINE and other NLM databases. Improvements included access to more databases, additional assistance to users in selecting appropriate search terms, and improved procedures which allow users to send questions and comments to NLM staff, and save searches to be rerun later. In FY 1989, work was completed on the first Macintosh version of GRATEFUL MED which will make user friendly access to NLM's databases available to an additional segment of the biomedical community in early FY 1990.

Use of DOCLINE, NLM's automated document request system, is also on the rise. In FY 1989, more than 1.6 million document requests were entered in the system by 1,819 participating health sciences libraries in the Regional Medical Library Network. NLM itself received 227,841 interlibrary loan requests for documents, 11% more than the previous year. Use of NLM's telefacsimile service continued to increase. The Library received 3,364 fax requests; 1,461 of these were needed for clinical emergencies.

NLM's ability to provide access to the biomedical literature is dependent on the effectiveness of its programs for acquiring, preserving, cataloging and indexing. In FY 1989, the Library added 43,366 book and journal volumes and 699,816 other items (e.g., audiovisuals, microforms, software, pictures, manuscripts) to its collection. To ensure that the Library's stated collection development policies are being implemented successfully and that these policies serve the needs of health professionals and researchers, the NLM staff initiated a regular collection assessment program that will examine different subject areas and types of material each year. As a result of assessments conducted in FY 1989, NLM verified that its journal collection is appropriately comprehensive in the fields of DNA sequencing, immunology, and paleopathology.

NLM's preservation program continues to progress. In FY 1989, 5.7 million pages of brittle books and serial volumes were microfilmed. As part of the National Plan for Preservation of Biomedical Literature, NLM also issued its first cost-sharing contracts for preservation of unique biomedical materials held by other institutions. The first two recipients were Yale University Medical Library and the Louise Darling Medical Library at UCLA. During FY 1989, all U.S. publishers of titles indexed by NLM for Index Medicus and MEDLINE were surveyed about their use of acid-free paper. As a result, 333 titles or 11% of Index Medicus titles will be flagged in the published lists of journals that NLM indexes as being printed on acid-free paper.

In FY 1989, NLM cataloged 18,733 items, reducing its backlog of uncataloged books by 1,327 to a total of 7,868 items, most in languages other than English. A new, and more efficient PC-based cataloging data entry and maintenance system was developed for full implementation in early FY 1990. A record high of 372,978 articles was indexed for MEDLINE in FY 1989. Abstracts were entered in the database for 62% of these. NLM continued its policy of identifying articles with fraudulent or erroneous data by linking published retractions and errata notices to the citations for the original articles in

the MEDLARS databases. In FY 1989, this practice was expanded to include the linking of significant commentaries (e.g., those that cause serious doubt on the reliability of the information presented) to previously cited articles.

Database Access

In response to the Congressional mandate that NLM make its information services widely available at reasonable prices, accessibility has been increased. Last year over 4 million searches were performed of files at NLM and a like number through commercial information vendors. Some 42 medical schools and hospitals now mount subsets of the NLM databases and nine licensed commercial CD-ROM vendors are widely distributing MEDLINE and other databases nationally and internationally.

NLM continues to follow carefully the Congressional advise of its appropriation and authorization committees in pricing its products and services. In essence, the Federal government supports the creation of the MEDLARS system, and the users in the biomedical community pay the full costs to access the system. Foreign users, as non-U.S. taxpayers, pay a surcharge that represents their proportional share of the costs of creating the databases. Last year NLM collected revenues of $12 million and returned $5.2 million to the Treasury. The latter figure represents foreign user surcharges above the cost of access and the costs included in the pricing calculation that are already supported through appropriated funds. The revenues related to access and the cost of access are essentially equal.

Unified Medical Language System

The Unified Medical Language System (UMLS) project is a major NLM research and development effort designed to facilitate the retrieval and integration of information from many machine-readable information sources, including descriptions of the biomedical literature, clinical records, factual databanks, and knowledge-based systems. The lack of effective links among the different terms used to express similar concepts in different machine-readable databases is a fundamental problem that prevents health professionals from finding relevant information and impedes general progress on the development of effective medical information systems. The UMLS approach assumes that diversity will continue to exist and seeks to provide products that can compensate for differences in the vocabularies and coding schemes used in different systems as well as for differences in the terminology employed by system users.

In FY 1989, the UMLS project focused on the development of the initial version of the Metathesaurus, the central vocabulary component of the UMLS. Meta-1, as the first version of the Metathesaurus is called, will contain more than 60,000 biomedical terms representing approximately 30,000 concepts, plus records for an additional 50,000 names of chemical substances. Meta-1 will be available for public distribution in mid-1990. It is intended for use primarily by system developers in the development of user-friendly information systems for health professionals and biomedical researchers.

In addition to the substantial progress on building this basic UMLS component, in FY 1989 the UMLS project resulted in the development of prototype systems, enhancements to existing systems, production of research tools, and studies that will provide insight into the information seeking behavior of NLM's user populations.

Computer-Based Educational Resources

Recent advances in optical disc and computer technology make possible new approaches to teaching and learning in the medical sciences. Only a few years ago, education that inherently required direct reference to pictures such as radiology, pathology, and hematology could be supported only by large collections of "hardcopy" visual materials that were expensive to create and maintain and could only be available to students at restricted times and places. For example, the standard learning tool in radiology has been a collection of about 6,000 films, copies of which cost medical schools over $25,000. Further, real-life, real-time simulations of medical events and techniques have been almost non-existent. The advent of relatively inexpensive pictorial and audio databases recorded on optical discs and of powerful microcomputers now make it possible to support almost all learning with technology-based systems. This technology which can support creation of core curricula delivered by computers and optical discs, is currently field-testing a prototype curriculum in one subject area.

These same technologies are capable of presenting realistic patient and laboratory simulations that permit students to make errors in diagnosis or patient management without endangering anyone's health. NLM-supported researchers have developed programs of this type which are being demonstrated to the medical education community. Plans include a more pervasive demonstration of the models to medical school facilities and wide distribution of the methods and materials to medical schools that are engaged in concerted efforts to revise curriculum to include problem oriented patient centered education.

Toxicology Information

Special information retrieval capabilities for those who must respond to chemical emergencies have been developed and are being field-tested in 13 States. The Toxicology Information Program, in collaboration with the Emergency Response Team of the Agency for Toxic Substances and Disease Registry (ATSDR), has built a microcomputer workstation (ANSWER) that can access and search some 500 databases on many Government and private sector systems. Users do not need to know the intricacies of searching these databases, the workstation handles the details of searching in the various computer systems. In order to make the workstation portable and thereby usable in remote emergency sites, a subset of the Hazardous Substances Data Bank (HSDB) augmented with emergency medical information has been placed on CD-ROM and stored in the workstation to allow local searching. The workstation has also been linked to the National Oceanic and Atmospheric Administration's weather information. This will facilitate decision-making when the dispersion of fumes or clouds of gases, resulting from a chemical

spill are a problem. All these capabilities have been packaged into a high-speed portable computer that is being field-tested by state health departments and poison control centers in 13 states under the auspices of ATSDR.

Management Improvements

Developed in accordance with Executive Order 12552 and subsequent OMB instruction, government-wide plans are developed that target government activities for productivity improvement measurements. The NLM's document delivery function, located within the Library's Public Services Division (PSD), is included in the NIH productivity improvement plan. PSD responds to thousands of document delivery requests from remote users throughout the country and abroad for biomedical information from the Library's collection of scientific monographs, journals, and audiovisual materials.

In order to respond to the increasing public demand for documents, the NLM conducted a management review of the delivery function. As a result, several improvements were implemented to improve the effectiveness and efficiency of the service. These included contracting out parts of the process (i.e., photocopying and reshelving) and modifying DOCLINE, the online system that routes a document request to NLM automatically, thereby reducing the amount of online maintenance performed by NLM staff. Quality and timeliness measurements have improved, while costs have remained constant.

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AIDS Information Initiatives

The NLM AIDS Program

Research results are of little value if they are not easily accessible to scientists and clinicians, and at no time in history has this been more evident than with the AIDS epidemic. The recently enacted Health Omnibus Program Extension of 1988 (P.L. 100-607) calls for NLM's involvement in the establishment of a "data bank on information on the results of research with respect to acquired immune deficiency syndrome conducted in the United States and other countries." NLM has laid the foundation for such a data bank by initiating three new databases, AIDSLINE; AIDSTRIALS; and AIDSDRUGS; expanding the coverage of AIDS-related organizations in the Directory of Information resources online (DIRLINE) file; and improving and increasing the frequency of its recurring AIDS Bibliography.

Recent Accomplishments

During the past year, a number of improvements were achieved. The AIDSLINE database was expanded with references from two other NLM online files--CANCERLIT and the Health Planning and Administration database. AIDSLINE was made accessible via GRATEFUL MED and tape distribution and Selective Dissemination of Information (SDI) service was implemented. Initial versions of AIDSTRIALS, covering PHS sponsored clinical trials; and AIDSDRUGS describing the drugs being tested in these trials and their known side effects, became available online in September 1989.

Future Plans

These steps represent only a beginning in developing a comprehensive AIDS information service. To ensure timely dissemination of scientific and medical information concerning this important disease to the biomedical community, a comprehensive AIDS information service is needed to provide scientists, physicians, and other health professionals faster access to more complete U.S. and international information on the AIDS research, diagnosis, treatment, control, and prevention areas. Plans are under way by NLM to: 1) improve the currency of information in AIDSLINE by incorporating more abstracts of presentations at AIDS-related meetings; 2) incorporate into AIDSLINE references to a broader range of publications possibly including those from non-NLM databases such as BIOSIS, Psychological Abstracts, and Sociological Abstracts; 3) enhance its existing information retrieval systems and investigate gateway access methods to connect its AIDS Information Service with relevant AIDS information resources available in other governmental, private sector, and international systems; and 4) initiate a series of special AIDS bibliographies, in addition to the current general AIDS Bibliography, that will be focussed on particular topics and audiences.

National Library of Medicine

Extramural Programs

Authorization: Indefinite

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$23,318,000	$23,991,000	+673,000

Purpose and Method of Operation

NLM's assistance programs are the unique Federal focal point for a nationally coordinated effort to make the full range of health knowledge available when and where it is needed and in a form which assures its proper interpretation and effective application. As biomedical research and its implication for clinical decisions become increasingly complex and prodigious, the effective mechanisms for organizing, retrieving, integrating, and using this information also become more complex and important. NLM assistance awards sponsor research investigations and research training in medical informatics and programs in the management and delivery of information, especially through systems integration and through interlibrary cooperation, and in the synthesis and interpretation of biomedical literature. NLM's distinct, but interrelated, grant and contract programs complement one another in achieving the overall goal of improved health care through the rapid, efficient, and effective communication of knowledge.

Rationale for Budget Request

The FY 1991 budget request for NLM's Extramural Programs is $23,991,000 which will support approximately 105 awards. This represents an increase of $673,000 over the FY 1990 appropriation.

Medical Library Assistance
Title IV, Part D, Sections 469-477, PHS Act
(Authorization expires September 30, 1990)

Integrated Academic Information Management System (IAIMS) Program

Integrated Academic Information Management Systems (IAIMS) are institution-wide computer networks that link and relate library systems with individual and institutional databases and information files, within and external to the institution, for patient care, research, education, and administration. Resource grants have been made to assist medical centers and health science institutions in planning and development projects that will lead to the implementation of IAIMS. The overall goal is to create organizational mechanisms within health institutions to manage more effectively the knowledge of medicine, and to provide for a system of comprehensive information access.

Using the Resource Project Grant mechanism, NLM has provided support for 1) institution-wide IAIMS planning and policy analysis, 2) model development and testing, and 3) implementation of detailed, tested plans for a full-scale IAIMS.

Some of the functions undertaken by grantees during planning include the preparation of a 10-year strategic plan for the institution, development of an institutional information policy, assessing the technological capabilities of the institution, and defining the information management needs and requirements. From these activities an IAIMS plan is created which serves as the guide for the second phase of activity, model development.

In Phase II, IAIMS concepts are being tested on a small scale in research, education, and/or patient-care areas. Health science institutions that have completed an IAIMS plan and can demonstrate examples of successful modeling of critical elements of their plan throughout Phase II support, may request, in the next competition in 1990, NLM assistance to proceed with full-scale IAIMS implementation in a Phase III award.

During the past year, 13 IAIMS planning and model development projects were active, including those having received grant awards in previous years. IAIMS Phase I planning was under way or nearing completion at the American College of Obstetricians and Gynecologists, Dartmouth College, Harvard University, Rhode Island Hospital, the University of Michigan, and the University of Pittsburgh. IAIMS Phase II model development and testing began at Baylor College of Medicine; was under way at Duke University and the University of Cincinnati; and was near completion at Columbia University, Georgetown University, the University of Maryland, and the University of Utah.

The Baylor College of Medicine is the newest institution to receive NLM support for the Phase II activity, having successfully completed an IAIMS planning grant. Their developmental efforts will concentrate on creating and testing an advanced information system for researchers and clinicians called "The Virtual Notebook." The "Notebook" will feature a scheme for representing

complex information structures, a communication manager for facilitating task assignment and coordination, and a facility for automatically importing relevant information from external sources such as libraries. The Virtual Notebook will be tested in four settings at the university.

Three institutions became the newest members of the select group receiving NLM support for information management large-scale systems. IAIMS Planning grants were awarded to Dartmouth College, and the Universities of Michigan and Pittsburgh.

Medical Library Resource Grants

Resource Grants assist public and private, non-profit health science libraries to establish, expand and improve library resources and information services to health personnel engaged in education, research and patient care. As stated in NLM's Long Range Plan, "The world's knowledge base is shifting inexorably from a paper to an electronic base." In accordance with this trend, the Resource Grant Program has changed focus to concentrate upon utilizing computer and communications technology to gain access to information resources and services.

Based upon the advice of NLM's Board of Regents and a panel of non-federal experts, the Resource Grant Program is restructured to offer: 1) an Information Access Grant to small- and medium-size hospital libraries and 2) an Information Systems Grant to larger hospitals and academic health centers. The Information Access Grant, which is available to both single institutions as well as consortia, supports projects proposing to improve access to information resources utilizing computer and communications technologies. The Information Systems Grant fosters networking, linkages, connectivity and integration -- all towards improving the information infrastructure through computer and communication technologies.

Research Grants in Medical Librarianship and Medical Information Science

The expansion of the international literature of the health sciences reflects the steadily expanding endeavors of the biomedical community which numbers not only investigators of biological phenomena, but also those who study the social and economic dimensions of health care. The implications of an enormous bibliography engage the attentions of those who seek better means of keeping libraries current in their access to medical literature and of those who seek to understand better the attributes of medical information, bibliography, and scholarship. The goal of these studies is to maximize the contributions of the nations' libraries to a fully informed health professional community, to explore new ways of better utilizing technology, and to develope information services based on clearly identified information related behavior.

In past years, these grants have led to advances in computer assisted indexing, to modern computer processing for library operations, and to useful comparisons of different literature retrieval techniques. Work is now continuing on a wide ranging examinations of medical literature and its access

in an academic medical center. This research is yielding new understandings of considerable interest to academic medical centers, especially those who participate in NLM's Integrated Academic Information Management Systems initiative.

Research Training in Medical Informatics and Biotechnology Information

NLM supports predoctoral and postdoctoral research training in the fields of medical informatics and biotechnology information. There is a need for qualified, talented investigators, well-equipped to address fundamental issues in the management of health knowledge. The training curricula are multidisciplinary, involving medicine, the cognitive sciences, information science, and computer science. Each training site offers an excellent setting for didactic instruction; involvement in major, ongoing health computer science studies; and opportunities for work in advanced information science research.

In recent years, a community of workers in medical informatics and biotechnology information has become established, with professional linkages extending among numerous cognitive disciplines. As the field has grown, investigators have shifted attention from using computers as tools to gaining better understanding of the cognitive processes and problems. It is now clear that fundamental issues of the role of knowledge, rather than studies of technological application, require probing scientific investigation.

Subsequent to their training period, these newly trained investigators will contribute to the growth of science by their studies of the role of knowledge in professional life, by analyses of the structures for managing knowledge, and by advancing the frontiers of the computer sciences for organizing, retrieving, and utilizing health knowledge.

Publication Grants

This productive program furnishes short-term support to prepare and publish not-for-profit biomedical studies for U. S. health practitioners, educators and research scientists. Publications funded include critical reviews and monographs on current and past developments in medical services and research; publications in health information science and medical informatics; secondary literature tools (handbooks, atlases, etc.); translations of important foreign-language monographs; and proceedings of significant health research symposia. Among the recent studies resulting from prior Publication Grant support is a comprehensive overview on the development of American hospitals in the twentieth century. This book draws upon a broad range of source materials in exploring major political, social, technological and economic influences upon U. S. hospitals as institutions. The low-cost Publication Grant Program is one of the very few sources of support for non-profit, scientific publications which synthesize developments in health research and practice for American health professionals.

Regional Medical Library (RML) Contracts

The purpose of the Regional Medical Library Network is to improve and equalize access to medical information throughout the United States by linking health professionals and researchers to the resources they need irrespective of their geographic location. The network includes health sciences libraries of all sizes in all parts of the country. In each of seven multi-state regions, NLM has contracted with a distinguished medical library to coordinate a regional document delivery program, develop outreach services to health professionals in areas without adequate library services, promote resource sharing among health sciences libraries, encourage and support the use of online services within their regions, and foster the development of innovative services to health professionals. The seven Regional Medical Libraries (RMLs) are supported by more than 120 large resource libraries, generally in medical schools, and many hospital and special libraries, individually and in effective consortia.

The RML network performs a major role in the dissemination of the results of biomedical research to health care practitioners. The existence of a functioning system of thousands of actively cooperating health sciences libraries is a singular achievement in both regional cooperation and nationwide networking. The RML program has also improved access to biomedical information in under served areas through decentralization of collections and services. The RML network has equalized access through efforts to establish national performance standards and service fees. It has promoted the diffusion of online technology development and use through extensive consultation and training activities. In addition, the RML program supports research and experimentation which may lead to improved methods of delivering needed information to U.S. health professionals.

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Medical Informatics

Title III, Part A, Section 301, PHS Act

Medical Informatics Research

Modern health knowledge in its volume and complexity far outstrips human abilities to integrate and exploit it fully for health care. The goal of the comparatively new discipline of medical informatics is to discover new ways of representing and retrieving biomedical knowledge in the context of computer and communications technologies. Investigations in this field range over the computer sciences, communications technologies, behavioral disciplines, and decision science, all within demanding clinical or biological domains.

NLM's support for medical informatics research has fostered contributions to medicine from such research areas as artificial intelligence, digitized and animated imaging, decision analysis, and database design. In several recent projects, the combination of artificial intelligence and decision analysis represents a synthesis of major significance for the elaboration of clinical decision support or medical consultation systems.

The development of interactive expert systems is one of many promising avenues of research effort. These systems can function in relation to or as a component of large scale medical information systems. They offer promise of connecting widespread communities of medical specialists through electronic networking and they raise interesting perspectives for health professionals education. Research results so far indicate that there is a sound basis for further, successful advances, although the tasks involved are demanding. Talented and enthusiastic investigators are reaching scientific maturity, well prepared by NLM's training programs. NLM's highly regarded initiative for Integrated Academic Information Management Systems suggests that for medical informatics research, there now exists a supportive and productive organizational structure in academic medicine.

Biotechnology Information Research

In biotechnology, more than any other area of the life sciences, the staggering volume of molecular data and its cryptic and subtle patterns have led to an absolute requirement for computerized databases and analysis tools. The rapid growth of research data has been accompanied by a proliferation of highly specialized databases, built independently and using dissimilar computer systems, having incompatible searching methods, and few conceptual linkages between them.

The building of better biotechnology databases is complemented by improved methods of information retrieval and analysis from those databases. NLM has a program of grants for computer analysis of molecular biology data. Its scope is quite broad and includes research into methods and algorithms for improving the efficiency of information retrieval and improving the efficiency of analytical operations which are computationally intensive, such as those which cannot be performed in linear time. Research applications to develop

expert systems for annotating and linking databases are invited, as are proposals for work on algorithms for structure function prediction. Software development for newer machine architectures is supported as well, including molecular analysis by neural net techniques, and multiprocessor programming

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National Library of Medicine

Intramural Programs

Authorization: Indefinite

Budget Authority:

1990 Appropriation		1991 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA
434	$455,811,000	447	$58,922,000	+13	+3,111,000

Purpose and Method of Operation

NLM's intramural activities are carried out by four major components:

- Library Operations -- acquires and preserves books, periodicals, prints, films, recordings and other library materials pertinent to medicine; organizes these materials by appropriate cataloging, indexing and bibliographical listing; publishes and makes available the catalogs, indexes and bibliographies; makes the literature available through loans, photographic or other copying procedures; and provides reference and research assistance. In addition, Library Operations assists in publicizing the availability of NLM products and services.

- Lister Hill National Center for Biomedical Communications -- the research and development arm of the NLM, explores the use of computer, communication, and audiovisual technologies for the purpose of improving the organization, dissemination, and utilization of biomedical information.

- National Center for Biotechnology Information -- creates automated systems for knowledge about molecular biology biochemistry, and genetics; performs research into advanced methods on how to handle information about the vast number of biologically important molecules and compounds; enables those engaged in biotechnology research and medical care to use the systems and methods developed; and coordinates efforts to gather biotechnology information worldwide.

- Toxicology Information Program (TIP) -- develops computerized databases in the fields of toxicology, pharmacology, and the environmental sciences and makes such information readily available to industry, academia, and Federal agencies. TIP is one of the Nation's most important sources of information for emergency response to toxic chemical spills and the release of health and environmental hazards.

Rationale for the Budget Request

The FY 1991 budget request for Intramural Programs is $58,922,000. This is an increase of $3,111,000 above the FY 1990 appropriation which will provide for increased operation costs in FY 1991. The budget request will provide for: payraise, FTS and other built-in increases for personnel and basic operating program requirements including increased costs of printing indices to the biomedical literature, services provided centrally and procuring supplies and materials. For example, NLM's management fund costs increase significantly from $8,241,000 in FY 1990 to $8,712,000 in FY 1991 Literature acquisition would receive a $587,000 increase to partially offset the soaring costs of obtaining the world's biomedical literature.

For FY 1991, the total amount requested for Intramural Programs includes $36,552,000 for Library Operations; $11,734,000 for the Lister Hill National Center for Biomedical Communications; $5,989,000 for the National Center for Biotechnology Information; and $4,647,000 for the Toxicology Information Program.

Library Operations

Library Operations carries out NLM's basic mission - to collect, organize, and provide access to the world's biomedical literature in support of the progress of medicine and the improvement of public health. The primary functions of Library Operations are to acquire and preserve the biomedical literature; to organize this literature through authoritative cataloging and indexing; to disseminate authoritative NLM bibliographic records in publications, online files, and other machine-readable forms; to lend or copy documents in the NLM collection as a back-up to document delivery service provided by other U.S. biomedical libraries; to provide reference and research assistance to health professionals; and to maintain an active program of scholarship in the history of medicine.

To improve the effectiveness and efficiency of NLM's unique biomedical information services, Library Operations makes regular and extensive use of advanced technology and conducts periodic evaluations of its programs and services. The Library also directs the Regional Medical Library Network and cooperates with the Library of Congress and the National Agricultural Library to enhance the general level of library service available in the United States.

Acquisition

The NLM collection currently contains more than 4.7 million items, including printed books, journal volumes, theses, pamphlets, audiovisuals, computer software, microforms, prints, photographs, and manuscripts. Library Operations staff select materials for the NLM collection according to the guidelines in the Collection Development Manual of the National Library of Medicine, endeavoring to identify and acquire as soon as possible new and retrospective literature in all areas of biomedicine. In FY 1989, NLM added 43,366 volumes and 699,816 other items (e.g., audiovisuals, microforms, software, pictures, manuscripts) to its collection.

During the past year, the Library established a regular collection assessment program that will ensure a more systematic examination of how successful NLM has been in implementing its collection development policies and how well these policies serve the needs of health professionals and researchers. Specific projects undertaken this year included assessments of parts of NLM's collection in the fields of DNA sequencing, immunology, and paleopathology, a review of general chemistry journals held by NLM, and the design and initiation of a comprehensive evaluation of NLM's dermatology collection. Results to date indicate that NLM's serials collection is appropriately comprehensive in the fields of DNA sequencing, immunology, and paleopathology.

Collection Preservation and Maintenance

Library Operations' preservation activities include: preservation and maintenance of NLM's own collection; support for the preservation of important biomedical literature not held by NLM; and promoting the use of more permanent materials in new biomedical publications. In FY 1989, NLM's preservation microfilming contractor filmed about 5.7 million pages of brittle books and serial volumes. To support its inhouse preservation program, NLM awarded new contracts to review portions of NLM's serial and book collection to identify brittle volumes to be microfilmed, to inspect the quality of preservation microfilms, and to store NLM's preservation master microfilms off-site. (Separate storage of preservation and printing masters reduces the chance that both could be destroyed in a single disaster.) NLM also expanded and improved the automated systems supporting preservation activities. In FY 1989, NLM awarded the first two national preservation project contracts for preservation of important biomedical materials not held by NLM to Yale University Medical Library and to the UCLA Louise Darling Biomedical Library. NLM funds 50 percent of the cost of these projects; the recipient institutions fund the remainder.

Library Operations also continued to support NLM's campaign to educate publishers and the biomedical community about the need to use acid-free paper in new publications to limit the growth of the preservation problem facing health sciences libraries. In FY 1989, the Library, in conjunction with the Permanent Paper Task Force appointed by the NLM Board of Regents, mailed a letter to all U.S. and some foreign publishers of journals indexed in Index Medicus and MEDLINE requesting information about their use of acid-free paper. Beginning in 1990, all Index Medicus journals reported to NLM as both printed on acid-free paper and including a notice to that effect will be specially flagged in the List of Journals Indexed in Index Medicus, the List of Serials Indexed for Online Users, and SERLINE, NLM's online file of information on serial publications. A total of 333 or 11 percent of Index Medicus titles will include this flag in the 1990 publications.

Creation of Bibliographic Data

To provide authoritative and effective bibliographic control of the biomedical literature, NLM maintains and enhances the Medical Subject Headings (MeSH)® and the NLM Classification scheme for the shelf arrangement of library materials; catalogs biomedical publications in all formats; and indexes articles from selected biomedical journals. In FY 1989, Library Operations cataloged a total of 18,733 books, serials, non-print media, and Cataloging in Publication (CIP) galleys, using a combination of inhouse staff, contractors and interagency agreements with the Library of Congress. The inventory of uncataloged books was reduced by 1,327 to a total of 7,868 items, most in languages other than English. A new and more efficient PC-based cataloging data entry and maintenance system was developed and will be fully implemented in early FY 1990.

A joint Library Operations/Lister Hill Center project to create machine-readable cataloging records and linked videodisc images of all items in NLM's historical picture collection is proceeding rapidly. Initial abbreviated machine-readable records have been created for all pictures, and procedures for producing both master negatives and videodisc copies of the pictures have been established and tested. Upgrading the machine-readable records to fuller format is underway and actual filming of the picture collection.

With the assistance of the Literature Selection Technical Review Committee, an NIH-chartered committee, Library Operations is gradually increasing the number of journals indexed and accessible via MEDLINE. A total of 372,978 articles was indexed in FY 1989. Sixty-two percent of all citations entered into MEDLINE during the year contained abstracts. NLM now enters an English language abstract into MEDLINE for any indexed article in which one is present. NLM continues to call attention to retracted or corrected articles cited in MEDLARS and in FY 1989 expanded this practice to include the linking of commentaries (for example, those that cast serious doubts on the reliability of the information presented) to previously indexed citations.

Dissemination of Bibliographic Data

NLM disseminates its bibliographic data online, in various machine-readable formats, and in a series of publications ranging from Index Medicus, NLM's major index to nearly 3,000 biomedical journals, to Current Bibliographies in Medicine, which are relatively brief compilations of recent citations on specific topics of current interest.

NLM provides online access to 42 MEDLARS databases, including the MEDLINE and TOXLINE backfiles. In FY 1989, the Library's online users accounted for a total of 331,000 hours of online usage, 5.9 percent more than in FY 1988. This figure does not reflect use of MEDLARS data on the computer systems of the other domestic and international organizations that lease NLM's files. The number of online codes authorized to use NLM's online system continues to increase rapidly. At the end of FY 1989, there were 30,933 active codes, an increase of 49 percent from the end of the previous year. The special student code program continues to be very popular. There are now 5,142 institutional and individual student codes. Individuals now account for 48 percent of all code holders. Seventy-one percent of the individuals who received new codes in FY 1989 indicated an intention to use the GRATEFUL MED microcomputer front-end package to access NLM's online services. About 17,000 copies of GRATEFUL MED have been sold by the National Technical Information Service since the package was introduced in March 1986. Purchasers of GRATEFUL MED automatically receive new versions of the package as they become available. Version 4 of GRATEFUL MED for IBM PC and compatible microcomputers was issued in January 1989. Improvements incorporated in this version included: easy access to more databases, additional help in selecting appropriate MeSH terms, a Bulletin Board System that allows users to send questions and comments to NLM, the ability to save searches to be rerun later, and support for the use of a "mouse" with GRATEFUL MED. A tutorial disk developed to explain how to

use GRATEFUL MED effectively is now issued to all new or potential GRATEFUL MED users. Work was completed on the first version of GRATEFUL MED for the Apple Macintosh microcomputer, to be released early in FY 1990.

During FY 1989, NLM made several important improvements to its online services. DENTALPROJ, a database of ongoing dental research projects developed by the National Institute of Dental Research, became available on NLM's online services network in FY 1989. The ELHILL command language was extended to facilitate the submission of the same search to multiple MEDLARS databases. Access to NLM's system via commercial telecommunications networks was expanded to included Compuserve and Infonet as well as Tymnet and Telenet. As part of its continuing effort to provide more convenient administrative arrangements for access to NLM's online system, NLM now offers master account billing, which summarizes on a single bill usage for online codes issued to multiple users in a single institution. More than 70 master accounts have been established, covering more than 700 codes. The Library has also entered into experimental agreements with two institutions to test an annual flat-rate charge per online code.

During the past year, NLM continued its efforts to expand awareness of GRATEFUL MED and NLM's online services within the biomedical community. In addition to broadening its program of exhibits and presentations at meetings of health professionals and researchers, the Library trained a group of FASEB Summer Research Conference attendees to demonstrate GRATEFUL MED and NLM databases to their colleagues at summer conferences in Vermont and Colorado. The Library also designed a special short course on the use of GRATEFUL MED which is now offered regularly to NIH staff.

To provide the widest possible access to its authoritative data, NLM leases complete databases and subsets of selected databases in machine-readable form. There are now more than 80 organizations leasing MEDLARS data, including several commercial organizations that produce CD-ROM products from the data.

Reference Service and Document Delivery

During the past year, NLM received 61,840 requests for reference assistance, 64 percent from onsite users, 35 percent in telephone calls, and 1 percent in letters. Improved printed and video instructions in the use of specific reference tools and the introduction in late FY 1988 of "pathfinder" brochures designed to help onsite users find information in specific subject areas have reduced the number of questions NLM receives from onsite users. In FY 1989, NLM improved service to onsite users by providing access to CD ROM versions of the indexes to NTIS technical reports and the publications of the Government Printing Office. The Library also expanded onsite access to computer assisted instruction packages in the biomedical sciences.

NLM's document delivery service provides materials to remote requestors as a back-up to the service provided by other libraries in the Regional Medical Library Network and also to onsite requestors who are seeking items in NLM's closed stacks. In FY 1989, NLM received 227,841 interlibrary loan

requests, 11 percent more than received in the previous year. Seventy-seven percent of the requests received by NLM were routed by DOCLINE, NLM's automated request generation and routing system. NLM received 3,364 requests via telefacsimile transfer; 1,481 of these were for materials needed for clinical emergencies and were processed within two hours. At the end of FY 1989, there were 1,819 libraries using DOCLINE. They entered more than 1.6 million requests into the system during the year, of which 92 percent were filled. DOCLINE is now routing serial requests based on more than 1,120,000 SERHOLD records representing the holdings of more than 2,500 institutions. The percentage of these holdings statements in the format most appropriate for specific automatic routing has increased to 71 percent.

NLM received 186,513 onsite requests for documents in FY 1989, 11 percent less than the number received in FY 1988. Eighty-three percent of the onsite requests for materials from the NLM stacks were filled, 84 percent within 30 minutes of receipt. Since the implementation of NLM's automated patron registration and request logging system in February 1988, 16,041 people have registered to request documents onsite at the Library.

In July 1989, NLM increased the contract support for document delivery to include photocopying of articles for interlibrary loan and the overnight onsite photocopy service.

Special Historical Programs

The Library has an outstanding collection of rare books, manuscripts, pictures, theses, and historical pamphlets which is a unique and valuable resource to scholars throughout the world. To promote continued growth and increased use of this rich collection, NLM sponsors a number of special programs. In addition to historical research conducted by NLM staff, the Library has established a competitive Visiting Scholar Program, which invites a recognized historical scholar to spend six to twelve months at the Library. Participating scholars are expected to engage in research that will use NLM's historical collections extensively and to advise NLM staff in their areas of expertise. The Library prepares a number of historical exhibits each year, often in conjunction with professional associations and other government institutions.

Lister Hill National Center For Biomedical Communications

The Lister Hill National Center for Biomedical Communications (LHNCBC) is the computer research and development division of the National Library of Medicine. Lister Hill Center projects develop and use new computer and information science methods to manage the vast and growing body of recorded knowledge in the life sciences. The volume of scientific information in biology and medicine far exceeds that capacity of human beings to remember, analyze, and communicate, and computers have become indispensable information management tools in biomedical research, education, and practice. Research projects conducted and supported by the Center concern technology applications as diverse as the development and evaluation of expert systems designed to support practitioner decision-making and the electronic representation in three dimensions of human anatomy for more accurate instruction in clinical education.

Unified Medical Language System (UMLS)

NLM's UMLS project will result in the development of an increasingly intelligent automated system that understands the complex language of biomedical terms and concepts, and applies this understanding to help health professionals and scientists retrieve and organize information in computer files and accessible in computer databanks across the country. The goal of the UMLS is to assist the retrieval and integration of information from a variety of machine readable information sources, including descriptions of the biomedical literature, clinical records, factual databanks, and medical knowledge bases. UMLS will compensate for the differences in the terms used in these different systems and for the alternative terms used by users, themselves. Currently, few systems can link different files of data describing the published literature, and almost no systems support the linking of these files with automated clinical records, databanks, or expert systems. No precise mechanism serves to connect related information of the four different types.

The solution to this fundamental medical information problem is the development of a Unified Medical Language System (UMLS). UMLS will take the form of a series of data files containing linkages between various computer systems and vocabularies which already exist as national resources in medicine, and also will build automated tools that can be invoked by a variety of applications to interpret questions, classify new medical information, and provide the intelligent links necessary to retrieve information relevant to a particular inquiry. Lister Hill Center will continue its efforts in this area and has already assembled a multidisciplinary team of NLM staff and external consultants who have identified the general parameters of the problem, and compiled basic information about some of the key sources of medical information and the classifications currently in use. In addition, the Center has developed a mechanism for involving qualified researchers from throughout the country in the UMLS project. Mechanisms have been established also for the sharing of research results and the testing of software tools produced.

The program will distribute tools developed such as a Metathesaurus (a computerized catalog of medical concepts represented in various computer databases and systems).

Computer Based Educational Resources

Recent advances in computer and optical disc technology make possible new approaches to teaching and learning in the medical sciences. Until recently, education that required direct reference to pictures such as radiology, pathology, and hematology could be supported only by large collections of "hardcopy" visual materials that were expensive to create and maintain and could only be available to learners at restricted times and places. The advent of relatively inexpensive graphics and computer-based imaging recorded on optical discs, combined with powerful microcomputers now make it possible to support almost all visual and multi-media learning with technology-based systems.

Lister Hill Center staff promote awareness of and access to computer based educational resources for the health professions as well as engaging in research and development in areas of new technologies. Emphasis will be placed on the development of new medical image libraries on video and optical disks. Such videodisc projects which will allow use of these images for improvement in education of both physicians and patients, and for medical research.

The major new project is the development of a digital image library of a complete male and female human form. This "Visible Human" project will build a computerized three dimensional representation of the entire body, as derived from computerized tomography (CT), magnetic resonance imaging (MRI), as well as photographic sections of selected human cadavers. Such a library will provide an unparalleled opportunity to create computer programs and systems which demonstrate the complexities of human internal anatomy in a manner which allows the user to selectively rotate, dissect, and reassemble organs, tissues, and body regions on the computer screen.

Expert Systems Program

A research program in artificial intelligence concentrating on expert systems was established at LHNCBC in 1984. Expert systems are computer programs which combine knowledge of a particular subject area with inferencing mechanisms (e.g., "if-then" rules) enabling them to use this knowledge in problem-solving situations. Expert systems can be categorized in two primary types: systems to assist experts in coping with conditions of information overload, and systems for the transfer of expertise. The latter systems can amplify the accessibility of specialist-level expertise by encapsulating portions of this expertise and making it available when the human specialists are not. Systems of both types are under active development at the Lister Hill Center.

One focus of the Expert Systems Program is the continuing development and evaluation of the AI/RHEUM consultant system in rheumatology, one of the world's largest medical artificial intelligence systems. AI/RHEUM is the best known of a series of knowledge-based medical consultant systems using the criteria table form of knowledge representation pioneered by NLM researchers. The power, simplicity and flexibility of this representation are augmented by a new expert system shell written at NLM for the development of criteria-based reasoning systems. In its current state, the AI/RHEUM diagnostic system contains in its knowledge base information on 32 rheumatologic diseases. It reasons from nearly a thousand patient findings (basic information such as signs, symptoms, laboratory tests and radiographic observations) to distinguish among 32 diseases which affect bones and jones. It has several hundred text definitions (the "Tell Me More" knowledge source) available in a fraction of a second to explain those patient findings which might not be familiar to its intended users. In addition, the system offers direct access to a "Show Me More" videodisc image bank illustrating specific rheumatologic findings. The first of the AI/RHEUM videodiscs contained about 1,900 images. In a two-year project involving multiple subject experts and colleagues and institutions in five states, Expert Systems Program staff working with the Audiovisual Program Development Branch of LHNCBC have produced a new rheumatology videodisc image bank with 6,300 still frames and 15 minutes of motion video sequences to help physician users accurately make patient observations otherwise difficult to illustrate.

Machine Learning Project

The need for this work arises from the explosive growth of biomedical information, and the parallel explosive growth in the number of analytical tools and techniques applied to that information. The National Library of Medicine has long recognized the need for automated assistance to help researchers and clinicians gain access to the increasing number of databases available and the massive amount of information. However, dramatic improvements in automated knowledge manipulation, analysis and inference will be soon necessary. Programs such as expert systems have already moved from the manipulation of information toward the manipulation of knowledge. The goal of the Machine Learning Project is to create computer programs that not only manipulate knowledge, but can also acquire it themselves. Ideally, a researcher or clinician with a question should be able to have a machine learning program identify where to find relevant information, retrieve that information (possibly from multiple data sources), and analyze and assemble the information into a complete, accurate and comprehensible representation of the desired knowledge.

In a world of rapidly advancing knowledge, computer programs will have to do more than retrieve information when asked. Once a user has specified a question of interest, a machine learning program should be able to continuously and intelligently track evolving knowledge sources for potentially relevant information. When the program finds relevant information, it should automatically assemble, analyze and send that information to the questioner.

Natural Language Systems Project

Natural Language Systems (NLS) research concerns the issues implicit in developing natural language processing systems for improved access to biomedical information in computerized databases. The problem may be viewed as the challenge of teaching computers to read and understand the technical language of written English. The research questions lie at the intersection of the fields of computer science, information science, and linguistics and involve methods and approaches used in all of these fields.

A major emphasis of the project is the development of SPECIALIST, an experimental system for parsing, analyzing, and accessing biomedical text. The parsing system includes morphological (word forms), syntactic (the structure of the English language) and semantic (how word meanings vary depending upon context) information and is supported by an extensive lexicon (word list). The parser currently gives a two-level output as it analyzes sentences. The first is a "parse tree" which shows the detailed structure of phrases and sentences; the second is a representation which more clearly shows the logical relations between elements in the sentence. NLS staff members have recently also begun the in-depth analysis of a sample of MEDLINE abstracts with the goal of establishing criteria for the automated analysis of the information structure of biomedical abstracts.

Machine-Readable Archives in Biomedicine (MRAB) Program

In a recently completed research program, the Electronic Document Storage and Retrieval Project, LHNCBC addressed the problem of efficiently converting book and journal pages to electronic computerized images. Such a technology promises an alternative to traditional photographic means of preserving library materials. However, Electronic Imaging offers the potential for far greater functionality than simple storage of pictures. It allows the creation of vast machine-readable text/image databases in very compact space (the equivalent of 350,000 to 400,000 document pages on a single 2 GB optical WORM disk, or about 50 million pages on a 128-disk jukebox), the capacity of rapidly and randomly navigating through this store, the ability to apply library processing (indexing and cataloging) to parts of the older literature which were not originally created as computerized resources.

A new research and development program is investigating the technologies involved in the processing of page images to extract the meaning represented by the "dot patterns" in the image. Such a program will demonstrate the potential for making the biomedical literature available in compact and accessible electronic form, and the technology to build computer-manipulable databases from information that is currently available only on printed pages. It will also support efforts to preserve the nation's biomedical literature since using optical storage would allow the nation's medical libraries to replace their brittle documents with more accessible and smaller optical disk storage devices. The availability of the rare and embrittled material in machine-readable form will allow it to be indexed and cataloged to levels that are more sophisticated and useful than currently possible. The program will design and develop a prototype system to demonstrate the feasibility of

creating, maintaining and accessing a machine-readable archive of documents; it includes components of image analysis and computerized character recognition, as well as refinement of methods for compact storage of large volumes of data, and its automated transmission over high speed computer networks.

National Center for Biotechnology Information

The National Center for Biotechnology Information (NCBI) was established by Public Law 100-607 in November, 1988, as a division of the National Library of Medicine. The establishment of the NCBI reflects the importance of developing new information technologies to aid in the understanding of the molecular processes that control health and disease. The Center has been given the responsibility to: 1) create automated systems for storing and analyzing knowledge about molecular biology, biochemistry, and genetics; 2) perform research into advanced methods of computer-based information processing for analyzing the structure and function of biologically important molecules and compounds; 3) facilitate the use of databases and software by biotechnology researchers and medical care personnel; and 4) coordinate efforts to gather biotechnology information worldwide.

The NCBI has created an NIH intramural research program and presently over 20 senior scientists, postdoctoral fellows, and support staff are conducting basic and applied research in molecular biology, biochemistry, genetics, biophysics, structural biology, computer science, and mathematics. The biotechnology information program will continue to be responsive to the needs of the biology research community and apply computer methods judiciously to their database and analytical problems.

The NCBI will continue to develop the GenInfo database concept, using NLM staff to generate a 'backbone' sequence database and build linkages to existing biological information resources. The database enhancement efforts will include collaboration with other NLM divisions in augmenting the MEDLINE indexing of nucleic acid and protein sequence data, in connecting the indexing vocabulary to keywords currently used by the GenBank and PIR sequence databases, and in building a new biotechnology citation database as an extension to MEDLINE. The Center will also continue to support the Database of Biotechnology Information Resources organized by Specialized Information Services. Collaborations with the Department of Agriculture and the U.S. Patent and Trademark Office will provide additional sequence data for the NLM GenInfo database.

Research and development in information retrieval and analysis tools will be a major effort intensified by the availability of national networking, high-performance workstations, and standardization of windowing interfaces. The NCBI is developing standards for the interchange of sequence, genetic and physical map data as well as computerized tools for distributed data access and analysis. Access to the databases developed at the NLM and linked to other key information sources will be provided to the research community through high-speed (Internet) and public data networks. In the area of information resources, the NCBI will use contract and cooperative agreements to support key molecular biology databanks located throughout the country.

Support of workshops and scientific meetings are considered a major responsibility of the Center as part of the NLM Outreach effort and will be supplemented with a visiting scientist program to provide close interaction with leading biologists, mathematicians, and computer scientists.

Toxicology Information Program

Throughout its history, the Toxicology Information Program (TIP), a major activity of the Division of Specialized Information Services, has maintained a linkage to the toxicology community through TIPCOM (Toxicology Information Program Committee), an advisory committee, which has been operated for the Library by the National Academy of Sciences (NAS). TIPCOM has been staffed by some of the leading toxicologists in the United States. Many of these scientists have also been active in the Society of Toxicology and other professional groups, and, thus, have been able to keep close track of the information needs of toxicology and related fields.

TIP's long-established TOXLINE databases provide an enormous storehouse of references on the health and environmental consequences of hazardous substances. The newer and rapidly growing Toxicology Data Network (TOXNET) has proven a successful approach to offering factual data about chemicals, their identity, safety and handling, toxicity, and environmental fate. TOXNET's Hazardous Substances Data Bank (HSDB) is also being used in chemical emergency response situations, such as highway spills involving dangerous substances.

As concern about health and the environment widens, information needs increase. Federal agencies are looking upon TIP and the NLM computerized search systems, ELHILL and TOXNET, as ideal vehicles to collect, search, retrieve and disseminate data in the areas of toxicology, environmental health, and hazardous materials, as well as in other arenas of the biomedical sciences. TIP welcomes this role and looks forward to retaining its strong ties with the scientific community while broadening its services to local governments and to the public.

Databases under ELHILL

CHEMLINE (Chemical Dictionary Online) is an online chemical dictionary and directory file which allows users to identify chemical substances via nomenclature and other identifiers, and to formulate optimum search strategies for other NLM files. Each chemical record has pointers to other files in the ELHILL and TOXNET systems that contain information about that chemical substance. Originally made available in January 1974 with about 59,000 records, the file now contains over 875,000 records describing chemical substances of biomedical or regulatory interest.

TOXLINE (Toxicology Information Online) is an online bibliographic retrieval service, produced by merging "toxicology" subsets from some fifteen secondary sources. During FY 1989, the TOXLINE files were regenerated and restructured so that TOXLINE and its backfile, TOXLINE65, now contain data only from sources which do not require royalty charges based on usage. Information from Chemical Abstracts, which does involve payment of usage royalties, is used exclusively to create two other online files, TOXLIT and TOXLIT65.

The four databases in the TOXLINE family of services now contain some 2,780,000 records. This represents more than a ten-fold increase in the number of bibliographic records since the original TOXLINE file was first made available by NLM in September 1972.

DIRLINE (Directory of Information Resources Online), is an online directory of organizations with information resources and subject expertise who are willing to provide information and help in response to inquiries. This database assists MEDLARS users by providing an alternative resource for information needs not met by bibliographic or factual databases. DIRLINE is comprised of 11 subfiles which provide information from sources which collect and maintain the information.

AIDS

Acquired Immunodeficiency Syndrome (AIDS) is a major public health crisis world-wide. The World Health Organization estimates that as many as ten million people are infected with the human immunodeficiency virus (HIV), which causes AIDS. The NLM is contributing to the Government's efforts in combating this disease by expanding its information services in this area.

The Health Omnibus Programs Extension Act of 1988 (HOPE, PL 100-607), mandated the development of several AIDS-related information services including a data bank on clinical trials and treatments. In response to that mandate, two new databases have been created. AIDSTRIALS contains descriptions of investigational clinical trials being conducted to test the safety and efficacy of various agents against AIDS and AIDS-related diseases. The information contained in this database is provided by the National Institute of Allergy and Infectious Diseases (NIAID) and the Food and Drug Administration (FDA). A complementary database, AIDSDRUGS, contains descriptions of the agents being tested in the clinical trials. The information for AIDSDRUGS comes from published literature and includes adverse effects, chemical/physical properties, synonyms, and drug interactions.

TOXNET and its FILES

The Hazardous Substances Data Bank (HSDB) is also supported, in part, as a Superfund activity with co-funding from the Agency for Toxic Substances and Disease Registry and NLM. Major enhancements included the addition of Express Updates with current literature from primary sources, and of Source Updates, i.e., data extractions from recent editions of standard literature sources, such as handbooks and textbooks. Both activities have significantly increased the amount of new data in the file, as well as the numbers of records enhanced with new data.

The Toxic Chemical Release Inventory (TRI) has quickly established itself as a file of major importance. TRI is mandated by the Emergency Planning and Community Right to Know Act (Title III of SARA). This database, compiled and maintained by EPA, contains environmental release data for over 325 chemicals, with the names and addresses of the industrial facilities reporting estimated

releases during 1987. TRI became publicly available on June 19, 1989, with considerable media attention. Public interest and online usage have been high.

The Chemical Carcinogenesis Research Information System (CCRIS), is maintained by the National Cancer Institute (NCI). This data bank contains test results from carcinogenicity, mutagenicity and tumor promotion studies.

The Registry of Toxic Effects of Chemical Substances (RTECS) is a data bank, based upon a National Institute for Occupational Safety and Health file by the same name, which NLM restructures for online searching. In December 1987, the RTECS file was made available on NLM's TOXNET system, with a newly structured unit record differing somewhat from the version previously available on ELHILL. RTECS now contains over 100,000 records.

The Environmental Mutagen Information Center (EMIC) bibliographic database is produced by the Environmental Mutagen, Carcinogen, and Teratogen Information Program of the Oak Ridge National Laboratory. It includes citations to publications that deal with the evaluation of all agents, except ionizing radiation, for genotoxic activity. EMIC is funded by the National Institute of Environmental Health Sciences and the Environmental Protection Agency. In FY 1987, the National Library of Medicine agreed to assume management of the EMIC database, including the responsibility to build, maintain, and provide public access to it via the TOXNET system.

The Environmental Teratology Information Center (ETIC) bibliographic database contains citations to publications concerned with teratology and developmental toxicology. ETIC is funded by the National Institute of Environmental Health Sciences, the Environmental Protection Agency, and the Agency for Toxic Substances and Disease Registry. In FY 1987, NLM assumed management of the building, maintenance, and public access to the database. In FY 1991, the scope of the database may expand to include additional aspects of developmental and reproductive toxicology. An advisory committee, the Teratology Information Users Group, is assisting NLM in developing the content of the ETIC database.

User Support Services

User support for all its online files is an ongoing TIP function. User Guides, FACT SHEETS, and the TOXNET Brief Guide are made available in addition to providing training on the use of its online files, both as a part of the MEDLARS Training Program, and for other users at special training sessions and at professional meetings.

Health Hotlines, a booklet which consists of a compilation of organizations with toll-free telephone numbers taken from DIRLINE, was updated and redistributed in April 1989. These organizations provide information and services directly to requesters. Health Hotlines has been a very popular and sought-after publication; over 40,000 booklets have been distributed to all sectors of the public, including libraries, health departments, newspapers, magazines, and private citizens.

In addition, special training in the use of the toxicology files was provided, in conjunction with the Agency for Toxic Substances and Disease Registry, to environmental health specialists from ATSDR and selected State agencies. To date, representatives from health agencies in 38 States and two U.S. territories have been trained. In addition, individuals from 11 occupational health clinics and the seven organizational members of the American Minority Professional Health Schools have taken this training.

During FY 1989, TIP developed TOXLEARN, a microcomputer-based training program for TOXLINE. It is designed to teach users how to search TOXLINE effectively. TOXLEARN is one of a series of microcomputer-based, self-instructional tools for selected MEDLARS databases. MEDTUTOR, a similar microcomputer-based training program for MEDLINE, was also completed. Perhaps the most important design feature of both TOXLEARN and MEDTUTOR is their systematic practice and diagnostic feedback. These programs provide an alternative or augmentation to formal classroom training.

Microcomputer Workstation for Chemical Emergency Response

TIP is collaborating with the Agency for Toxic Substances and Disease Registry (ATSDR) to build a portable, microcomputer-based workstation that can provide information assistance to emergency response teams (ERT) responding to hazardous chemical releases or spills. The operational prototype, known as ANSWER (an acronym for ATSDR/NLM's Workstation for Emergency Response), is designed to facilitate easy access to useful information by ERT members during emergencies.

Biotechnology

The Directory of Biotechnology Information Resources (DBIR) was first offered, in January 1989, as an online file on TOXNET where it was assembled and is being maintained. Several months later it was also added as a component file to DIRLINE on ELHILL. Distribution of the file on magnetic media is now being evaluated. DBIR now contains over 1000 entries, describing many accessible resources in biotechnology and molecular biology. These resources include databases and services, organizations, repositories, reference publications, and sanctioned nomenclature committees.

A survey of industry, regulatory agencies and public interest groups, evaluating the need for a publicly-available data bank facility - labelled the Biotechnology Environmental Release Data Bank (BERD) - has been completed for NLM by a contractor. The affirmative results of this survey are currently being evaluated by the interagency BERD Working Group, chaired by TIP. The Working Group will provide advice concerning the need for such a facility to the Office of Science and Technology Policy of the Executive Office of the President.

Information Services to Other Agencies

As described above, TIP provides information and management support to the Agency for Toxic Substances and Disease Registry (ATSDR) by building and maintaining computerized information resources supportive of ATSDR's legislative mandates. NLM also continues to maintain and deploy other systems of data and information sponsored by various Federal Agencies.

TIP provided the Deputy Chair and committee management support for the Subcommittee on Information Coordination (SIC) of the Department of Health and Human Services' Committee to Coordinate Environmental Health and Related Programs (CCEHRP). TIP also represented NLM on numerous inter and intra-agency committees and working groups.

National Library of Medicine

Research Management and Support

Authorization: Indefinite

Budget Authority:

1990 Appropriation		1991 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA
90	$6,599,000	90	$7,003,000	---	+404,000

Purpose and Method of Operation

Research Management and Support funds the salaries and expenses of the staff who provide for overall administration and direction of National Library of Medicine programs, including the extramural grant and contract programs. Among the functions carried out in this activity are execution of basic administrative services; contracts processing and management; grants management and the scientific direction of NLM's extramural programs, financial and personnel management; coordination of equal employment opportunity activities; direction of NLM's international programs; public inquiries and management of the Library's publications; and operations research. NLM's planning and evaluation activities are also provided for in this activity.

Rationale for Budget Request

The FY 1991 budget request for Research Management and Support is $7,003,000 and represents an increase of $404,000 above the FY 1990 appropriation. This increase will provide for payraise and other personnel expenses, supplies, and basic operating administrative and scientific management requirements in 1991. Through this activity, NLM will continue to provide efficient and effective administrative support and management, and scientific direction for its programs.

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Professional History: 1963-1965, Instructor and Chairperson, Maternity Nursing Section, University of Kansas, Lawrence, Kansas. 1966-1967, Assistant Professor, School of Nursing, University of California, San Francisco, California. 1968-1971, Administrative Coordinator, First Year Undergraduate Program, School of Nursing, University of California, San Francisco, California. 1971-1975, Masters' and doctoral studies, University of Arizona, Tucson, Arizona. 1975-1987, Liaison Position: Director of Nursing Research, University Medical Center, Tucson, Arizona and Professor and Director of Research, College of Nursing, University of Arizona, Tucson, Arizona. 1987-Present, Director, National Center for Nursing Research, National Institutes of Health.

Professional Organizations: American Academy of Nursing, American Nurses' Association (ANA), ANA Council of Nurse Researchers, Arizona Nurses' Association, Sigma Xi, Western Society for Research in Nursing, Sigma Theta Tau, National Academies of Practice, Institute of Medicine

Honors, Awards: Kay Schilter Award, University of Kansas School of Nursing, 1961. Lucille Petry Leone Award, National League for Nursing, 1971. Wolanin Geriatric Nursing Research Award, University of Arizona College of Nursing, 1978. Sigma Theta Tau, Beta Mu Chapter, Award for Excellence in Nursing Education, 1980. Alumni of the Year Award, University of Kansas School of Nursing, 1981. Distinguished Alumni Award, Yale University School of Nursing, 1981. Nurse Scientist of the Year Award, American Nurses' Association, 1985. Elizabeth McWilliams Miller Award for Excellence in Research, Sigma Theta Tau International, 1987. Doctor of Science Degree, University of Maryland, 1988. Doctor of Science Degree, Medical College of Ohio, 1988.

29-452 O—90——26

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Detail of Permanent Positions

	1989 Actual	1990 Appropriation	1991 Estimate
ES-4	6	6	6
ES-2	1	1	1
Subtotal	7	7	7
GS/GM-15	27	27	27
GS/GM-14	38	38	39
GS/GM-13	71	71	72
GS-12	76	76	86
GS-11	62	62	63
GS-10	2	2	2
GS-9	43	43	43
GS-8	17	17	17
GS-7	54	54	54
GS-6	48	48	48
GS-5	32	32	32
GS-4	19	19	19
GS-3	3	3	3
GS-2	0	0	0
Subtotal	492	492	505
Grades established by act of July 1, 1944 (42 U.S.C. 207):			
CO-6	1	1	1
CO-5	2	2	2
Subtotal	3	3	3
Ungraded	2	2	2
Total permanent positions	504	504	517

New Positions Requested

NLM Intramural Research	Grade	1991 Number	1991 Annual Salary
Computer Scientist	GS-14	1	$ 50,342
Research Biologist	GS-13	1	42,601
Computer Scientist	GS-12	4	143,300
Research Biologist	GS-12	2	71,650
Medical Officer	GS-12	2	71,650
Technical Information Specialist	GS-12	1	35,825
Computer Programmer Analyst	GS-12	1	35,825
Librarian	GS-11	1	29,891
		13	$481,084

ADVISORY AND ASSISTANCE SERVICES

National Library of Medicine

In FY 1991 NLM's consultant services requirements total $262,000, an increase of $10,000 from the FY 1990 for anticipated mandatory increases. NLM utilizes consultant services in a number of functional areas as part of the continuing efforts to define and address the information needs of the medical community. Consultant services are utilized to obtain advice and assistance in very specialized areas.

The largest component of the consultant services funds is for advisory services of the Toxicology Information Program Committee (TIPCOM) of the National Academy of Sciences for NLM's Toxicology Information Program (TIP). TIPCOM reviews current TIP activities and provides advice on assessing and planning for the intermediate and long range goals of TIP.

NLM also utilizes consultant funds to obtain special expertise and consultation in areas such as literature collection and preservation, software development, and medical expert systems evaluation methodology development.

Advisory Committee expenses are also included in planned consultant services for continued funding of NLM's Board of Regents, the Lister Hill National Center for Biomedical Communications Board of Scientific Counselors, and Library Operations' Literature Selection Technical Review Committee.

NLM's internal controls for consultant services ensure that only those consultant services that are necessary and approved are procured. NLM programs are required to specify specific consultant services needs during the budget review process conducted by the Director of NLM. The Director approves the level of consultant services to be utilized. His decisions are then used as a basis to develop an annual consultant services plan and determine the level of a separate budgetary allotment for consultant services. The planned and actual obligations charged to that are utilized to monitor consultant services obligations.

TUESDAY, MARCH 20, 1990.

NATIONAL CENTER FOR NURSING RESEARCH

WITNESSES

DR. ADA SUE HINSHAW, DIRECTOR, NATIONAL CENTER FOR NURSING RESEARCH

DR. WILLIAM F. RAUB, ACTING DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DR. JANET HEINRICH, DIRECTOR, DIVISION OF EXTRAMURAL PROGRAMS, NATIONAL CENTER FOR NURSING RESEARCH

WILLIAM K. RUSS, EXECUTIVE OFFICER, NATIONAL CENTER FOR NURSING RESEARCH

CHARLES R. ZELLERS, BUDGET OFFICER, NATIONAL CENTER FOR NURSING RESEARCH

DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET

Mr. NATCHER. At this time we take up the budget request for the fiscal year 1991 of the National Center for Nursing Research. We have before the committee Dr. Hinshaw.

Dr. Hinshaw, before you give us your statement, tell us who you have with you there at the table.

Dr. HINSHAW. I would be pleased to, sir.

At my far left I have Mr. Charles Zellers, Budget Officer for NCNR; Mr. William Russ, who is Executive Officer for the national center, and Dr. Jan Heinrich, who is Director of the Extramural Research Programs.

I believe you know these two gentlemen.

Mr. NATCHER. Yes, we do. They are friends of ours.

Thank you, Dr. Hinshaw. We would be pleased to hear from you at this time.

Dr. HINSHAW. Thank you.

Mr. Chairman, I am honored to appear before you again to discuss the programs of the National Center for Nursing Research and the developing knowledge base for nursing practice.

The national center has made considerable advances in the past year: the award of the first four research center grants, establishment of a new collaborative intramural research program, completion of the second stage of our research training initiative, completion of the reports of the first two priority expert panels for the national nursing research agenda, development of research initiatives for each of those two priority areas, development of a rural health initiative, and the establishment of a new program in bioethics and clinical practice.

Since the prevention and care of low birthweight infants is a priority area of scientific challenge and potential for nursing research, a major initiative has begun. This research has four major foci:

preconception care, prenatal care, care of the infant in the hospital, and follow-up care of the infant and mother after discharge.

One NCNR-supported scientist is testing the effectiveness of prenatal and postpartum nurse home visitation services as a means of enhancing the health and well-being of unwed poor women and their first-born children. Visiting nurses will teach the young mothers to improve their diets, to identify pregnancy complications, to avoid risk factors such as smoking and drinking, and provide a social support system for helping them to maintain such behaviors.

They will also help them with caring for their babies, including cognitive skill development and emotional development. The nurses will encourage the mothers to return to school and to find employment after the birth.

For the mothers, the study will measure changes in prenatal health habits, risk behaviors, infant caregiving skills and other behaviors. For the children, the study will measure the occurrence of prematurity and low birthweight, several types of growth and nutritional problems, and instances of possible child abuse and neglect through emergency room and physician visits. The preliminary study to this particular project has shown positive outcomes and significant promise for the nurse home visitation services.

Improving the methods of caring for low birthweight infants in the neonatal intensive care units of our country is another priority area for NCNR. Physical care of these infants such as feeding, respiratory care, skin integrity and positioning need further study. This will be necessary in order to identify the optimal care practices during hospitalization and immediately following discharge. In December of 1989, NCNR issued a program announcement, in collaboration with NICHD, inviting applications to address these issues.

One of the other major health challenges facing our nation is, of course, the AIDS epidemic. We are strongly committed to research on the physical, psychosocial, and ethical problems central to prevention of HIV infection and the care of persons with AIDS, their partners and their families. We are especially pleased with the establishment of our new collaborative intramural research program initiated in 1990 in cooperation with NIAID and the NIH Clinical Center Department of Nursing.

The intramural investigators will conduct basic and clinical research in symptom management for AIDS patients, seeking to minimize the kind of harmful effects that come with infection and the treatment—side effects such as unintentional weight loss, fatigue, diarrhea, oral complications, anxiety, pain, and depression.

For example, as the NIAID medical clinicians and researchers treat asymptomatic HIV-infected persons with AZT or alpha interferon, NCNR nurse scientists will quantify changes in nutritional status and then develop nursing interventions to minimize the nutritional problems such as anorexia, nausea, and weight loss. As long as the HIV infection remains incurable and advanced treatments allow individuals to live longer, it is important to discover ways to decrease the morbidity, to assess and to help the patients manage the symptoms, to diminish the economic and personal costs of this infection and to promote an optimal quality of life.

One NCNR extramural investigator is studying health characteristics of infants of high-risk mothers who remain HIV antibody positive over a three-year period, as compared with infants who show no HIV antibody or who seroconvert from positive to negative.

Many of the high-risk mothers decline being tested for antibodies to the virus, but permit testing of their infants. However, HIV antibody testing of the newborns is not always reliable for detecting infants who carry the virus versus those who simply have the infected mother's antibodies. They may have only transient antibody and actually themselves be free of the virus.

Developing better methods of detecting which children are actually infected is going to be critical. It is also important for the care of these children to determine the symptomatology, the infection rates, and the developmental patterns. These are variables that the nurse investigators are following closely, particularly the developmental patterns. These findings will prove useful, we think, to the mothers and nurses who will be caring for these high-risk infants in the future.

The increasing age profile of the nation has focused growing attention on Alzheimer's Disease and other dementias, as well as on frailty and injuries among older persons. Particularly for nursing, there is great concern with the broader problems of family caregiving.

The Center is defining and prioritizing nursing issues related to formal and informal caregiving practices. We have issued a research training program announcement and a research support program announcement relevant to caregiving with Alzheimer's Disease and related disorders, as well as an announcement for reducing frailty in the elderly. This has been done with the National Institute on Aging.

The new Exploratory Center for Nursing Research at the University of Minnesota specializes in long-term care of the elderly, particularly factors which influence the autonomy and independent functioning of older persons. Studies include clinical nursing interventions for preventing falls among hospitalized elders, the assessment of needs for older persons after hospital discharge, and the mix of formal and informal caregiving services that can best be used for the home.

Behavioral research is a key part of the mandate of the National Center for Nursing Research and accounted for almost 47 percent of the Center-supported research in 1989. Our research in that area addresses the behavior of patients and care providers related to both health and illness.

The new Specialized Center for Nursing Research at the University of Pennsylvania emphasizes advancing care in serious illness, particularly behavioral research on patient care. One study characterizes the depressive signs and symptoms experienced by stroke patients at three points in time after occurrence of the stroke. The results of this research should give nurses, through the development of a new instrument for detecting depression early, the ability to make timely referrals for treatment. This has been a major aspect of that particular center.

The adequacy of health care in rural areas is a growing challenge to the nation. NCNR is working with other PHS agencies to develop a research and demonstration initiative that will address health care issues facing rural Americans, particularly with a focus on the special needs of minorities.

As a relatively new arm of the NIH, the NCNR must facilitate the development of young investigators for an expanding area of science. Emphasis has been placed on increasing the number of trainees, building postdoctoral programs and encouraging more minority nurse scientists. In 1989, the center supported 228 research trainees and research career awards, exceeding the second annual goal of our research training initiative. The third goal of 270 for 1990 has been adjusted to 257.

The NCNR has implemented an initiative providing special research opportunities for minority faculty and students. The center has funded positions for minority students on NRSA institutional training grants as well as special supplements for minority faculty and research assistants on research project grants.

The new Specialized Centers have been required to incorporate minority outreach into their research efforts. In addition, an ad hoc task force of minority colleagues advises the NCNR on strategies for facilitating research training for minority nurses.

As the base of knowledge for nursing expands, we are confident that health care will become better understood and more effective, and the quality of care for millions of Americans who receive care each year will be enhanced.

Mr. Chairman, the fiscal year 1991 budget request for the National Center is $35,127,000.

I will be pleased to answer any questions that you may have.

Mr. NATCHER. Thank you, Doctor.

[The information follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Statement of the Director
National Center for Nursing Research

Mr. Chairman, I am honored to appear before you again to discuss the programs of the National Center for Nursing Research, the current state of knowledge for nursing practice, and the challenges facing us in patient care and the promotion of health in this country.

The National Center has made considerable advances in the past year: the award of the first four research center grants; establishment of a new collaborative intramural research program; completion of the second step of the research training initiative; completion of the reports of the first two priority expert panels for the National Nursing Research Agenda -- on the nursing research needed for low birthweight infants and on patients with HIV infection; development of research initiatives for those two areas; development of a rural health initiative; and the establishment of a new program of research in bioethics and clinical practice.

Since prevention of and the care of low birthweight infants is a major area of scientific challenge and potential for nursing research, a major initiative has begun. This research has four major foci: preconception health, prenatal care, care of the infant in the hospital, and follow-up care of the infant and mother after discharge.

One NCNR-supported scientist is testing the effectiveness of prenatal and post partum nurse home visitation services as a means of enhancing the health and well-being of unwed poor women and their first-born children. Visiting nurses will teach the young mothers to improve their diets, to identify complications in pregnancy, and to care for their babies, including cognitive skill development and emotional development. The nurses will also encourage the mothers to return to school and find employment after the birth. For the mothers, the study will measure changes in prenatal health habits, infant caregiving skills, and other behaviors and skills. For the children, the study will measure the occurrence of prematurity and low birthweight, several types of growth and nutritional problems, and instances of child abuse and neglect. The preliminary study showed positive outcomes from the nurse home-visitation services.

Methods of caring for low birthweight infants in neonatal intensive care nurseries are another priority area for the NCNR. Physical care of these infants such as feeding, respiratory care, skin care, and positioning needs further study, to identify optimal care practices during hospitalization and after discharge. In December 1989 NCNR issued a program announcement, in

collaboration with the National Institute of Child Health and Human Development, inviting applications to address these issues.

The most ominous health challenge facing our Nation is of course the AIDS epidemic. NCNR is strongly committed to research on the physical, psychosocial, and ethical problems central to prevention of HIV infection and the care of persons with AIDS, their partners and families. We are especially pleased with the establishment in 1990 of our new Intramural Research Program in this field, in collaboration with the National Institute for Allergy and Infectious Diseases and the NIH Clinical Center.

NCNR intramural investigators will conduct basic and clinical research in symptom management of AIDS patients, seeking to minimize the harmful effects of the infection and treatments, such as unintentional weight loss, diarrhea, fatigue, oral complications, dementia, anxiety, pain, and depression. For example, as NIAID clinicians treat asymptomatic HIV-infected persons with AZT or alpha interferon, NCNR nurse scientists will quantify changes in nutritional status, and then develop nursing interventions to minimize nutritional problems such as anorexia, nausea, and weight loss. As long as HIV infection remains incurable and advanced treatments allow individuals to live longer, it is important to discover ways to decrease morbidity, to diminish the economic and personal costs of infection and treatment, and to promote an optimal quality of life.

An NCNR extramural investigator is studying health characteristics of infants of high risk mothers who remain HIV antibody positive over a three year period, as compared with infants who show no HIV antibody or who seroconvert from positive to negative. Many of the high risk mothers decline to be tested for antibodies to the virus but permit testing of their infants. However, HIV antibody testing of newborns is not reliable. Some infants who test positive later convert from seropositive to seronegative, and develop no symptoms associated with HIV infection. They may have had only transient maternal antibody and may be free of the virus. Developing better methods of detecting which children are actually infected is crucial to offering earlier, more effective care. Physiological and psychosocial growth and development measures as well as biological indices of HIV seroconversion are being tested, and may prove useful to nurses caring for high risk infants in the future.

The increasing age profile of the nation has focused growing attention on Alzheimer's Disease and other dementias, frailty and injuries among older persons, and the broader problems of family caregiving. The Center is defining and prioritizing nursing issues related to formal and informal caregiving practices. The Center has issued both a research training program announcement and a research support program announcement relevant to Alzheimer's Disease and related disorders, reducing frailty in the elderly, and issues in caregiving. One of the NCNR's new research centers focuses on related patient care issues with the elderly, for example, assessment of activities of daily living in determining the risk of falling in the elderly.

Some data suggest that informal caregivers (relatives, friends, or others who are not paid) experience extensive physical, emotional, and financial costs related to caregiving. One project focuses on refinement and testing of a model of caregiver perceptions of the burden and measures of the quality of caregiving. This study will assess changes in these relationships over time, to indicate points at which interventions by nurses may be most effective. This model should enable nurses to assist families in increasing the quality of care and identifying coping strategies.

The new Exploratory Center for Nursing Research at the University of Minnesota specializes in long term care of the elderly, particularly factors which influence the autonomy and independent functioning of older persons. Studies include clinical nursing interventions for aggressive behavior by cognitively impaired older people in nursing homes, prevention of falls among hospitalized elders, assessment of the needs of older persons after hospital discharge, and the mix of formal and informal caregiving services best for the home.

Behavioral research related to health is a key part of the mandate of the National Center for Nursing Research, and accounted for over one third of Center-supported research in 1989. Our research addresses the behavior of patients and care providers related to health and illness. Our new Specialized Center for Nursing Research at the University of Pennsylvania emphasizes advancing care in serious illness, including behavioral research efforts. One study characterizes depressive signs and symptoms experienced by stroke patients at three points in time after occurrence of the stroke. The location of the stroke within the brain will be related to the depressive symptoms observed. The results of this research should give nurses caring for stroke patients a tool for detecting depression, in order to make timely referrals for treatment.

We are especially interested in the development and maintenance of health promoting behaviors and the measurement of positive outcomes correlated to those behaviors. One of our grantees is studying the validity of the Health Promotion Model for explaining health promoting behaviors in adult populations of various ages with or without a recent catastrophic illness. The issues to be studied include exercise adherence among working adults, exercise adherence after myocardial infarction, ambulatory cancer patients' health promoting behaviors, and health promoting behaviors among older adults.

The adequacy of health care in rural areas is a growing challenge to the Nation. NCNR is working with other PHS agencies to develop a research and demonstration initiative that will address health issues of rural Americans, with a focus on the special needs of American Indians, native Alaskans and native Hawaiians, native Samoans, and other Pacific basin populations. Access to nursing services for rural populations is critical at this time.

NCNR is funding a study of home care, continuity of care and community support for older adults in two rural areas of Colorado. The investigator is describing the types and patterns of professional, family and community home health care services, the continuity of care from hospital discharge through home care, and problems with the services. It is expected that a comprehensive understanding of rural home care will provide a foundation for improved health care services to the rural elderly.

NCNR will be collaborating with the Agency for Health Care Policy and Research on the newly mandated Medical Treatment Effectiveness Program. The NCNR has emphasized the importance of quality of care and patient outcomes in its clinical research programs.

As a relatively new arm of the NIH, the NCNR must produce high-quality young investigators for an expanding area of science. Emphasis has been placed on increasing the number of trainees, building postdoctoral programs, and encouraging more minority nurse scientists. In 1989, the Center supported 228 research trainees and research career awards, thereby exceeding the second annual goal of our training initiative. The third goal of 270 for 1990 has been adjusted to 257.

The NCNR has implemented an initiative providing special research opportunities for minority faculty and students. The Center has funded positions for minority trainees on existing institutional training grants as well as special supplements for research assistants on research project grants. The new specialized centers have been required to incorporate minority outreach into their research efforts. An ad hoc task force advises the NCNR on strategies for facilitating research training for minority nurses.

As the base of knowledge for nursing expands, we are confident that health care will become better understood and more effective, and the quality of life for millions of Americans who receive care each year will be enhanced by the extensive research initiatives planned and conducted by the NCNR.

Mr. Chairman, the FY 1991 budget request for this Center is $35,127,000. I will be pleased to answer any questions that you may have.

Dr. HINSHAW. Mr. Chairman, I did shorten my remarks, so the full text will be provided for the record.

NATIONAL NURSING RESEARCH AGENDA

Mr. NATCHER. Thank you, Dr. Hinshaw.

Now, if you will, review for us the seven priority research areas you have identified and the timetable for your advisory groups to develop a research agenda for each.

Dr. HINSHAW. I would be glad to do so, sir.

The National Nursing Research Agenda was started in January of 1988. The first stage priorities were two: the prevention and care of low birthweight infants, and the prevention and care of HIV patients, their partners and families. Program announcements in both of those areas have gone out this year, and projects will be funded in 1990 and 1991.

The second stage priorities that are being developed by priority expert panels are long-term care of the elderly, symptom assessment and management, and information systems for improving nursing care for patient outcomes.

Those three priority areas will be completed in 1991. We will be putting out program announcements 1991 and 1992.

The stage three priorities are just beginning with the design of the priority expert panels, and they are twofold: health promotion in children and adolescents, and technology dependency across the lifespan. Those will be completed in 1992, and initiatives to encourage research in those areas will follow in 1992 and 1993.

Mr. NATCHER. Now, Dr. Hinshaw, are cost estimates attached to each of these research agendas?

Dr. HINSHAW. Yes, they are. They are being set by each priority expert panel. It is the experts looking at the science who are telling us how much is known in a particular area, where the weaknesses and gaps are, and how many research studies or research training awards need to be provided for each. Then we can determine the level of support in view of the budget.

Mr. NATCHER. How much research funding do you plan to set aside in 1991 specifically for these initiatives?

Dr. HINSHAW. That will be approximately $2.2 million, which is $1.1 or $1.2 million for each of the first two initiatives.

DECLINING AWARD RATE

Mr. NATCHER. From 1986 to 1990 you have issued about the same number of new grants each year, even though your award rate has dropped from 77 percent to 19 percent. Should we be very concerned, Dr. Hinshaw, that your award rate will drop further in 1991?

Dr. HINSHAW. We have been concerned with the dropping award rate. It obviously relates to a growing community and a growing number of applications which are competing successfully for the money in this area.

There is also a climbing average grant award amount, which we are aware of. That growth seems to reflect both the need to build the systems in which the research is being conducted, since nursing research is relatively new, and also the existence of a high propor-

tion of clinical research, as Dr. Raub explained a week ago when he was asked a similar question.

Mr. NATCHER. Why is a 12 percent downward negotiation rate necessary for new grants in 1990 when you are requesting a 19 percent increase in average grant costs?

Dr. HINSHAW. At that point we were projecting a different grant size and reduction rate. The 12 percent reduction is necessary because of the growth of our 1990 grants. I can provide a comparison of that for the record, sir.

[The information follows:]

COMPETING RESEARCH PROJECT GRANT SIZE IN FISCAL YEAR 1990

At the time the President's Budget for FY 1990 was formulated, the average size for NCNR's competing approved applications was estimated to be $190,800, and the reduction needed to achieve the number of competing awards in the request was 7.4 percent. This would have yielded an awarded average of $158,000.

At the time of the FY 1990 appropriation, the actual obligation figures became available for 1989. The size was larger than expected, and analysis of the growth from 1986 through 1989 showed an extraordinary rate of growth. It was necessary to raise the FY 1990 competing award estimates to accomodate this growth. The current estimate of the average size of the 1990 approved applications is $214,800. With a 12 percent reduction, the NCNR expects an awarded average size of $189,000 in FY 1990. These averages fall below the NIH-wide averages, despite the rapid growth in size within this new program.

Dr. HINSHAW. It is also related to the need to continue building the research training initiative, and the continuing climb in the average cost of the applications. The average award cost for all of our grants in 1987 was $134,500, and it increased to $160,300 in 1989, which compares to the $193,900 average cost of all NIH awards in 1989.

NCNR APPROVAL RATE

Mr. NATCHER. Your approval rate, Dr. Hinshaw, now approaches that of NIH as a whole. Is this appropriate for a relatively new field?

Dr. HINSHAW. Yes. In 1989, there was a 75 percent approval rate. We are estimated to be at around a 90 percent approval rate for applications in 1991. This shows, I believe, that an increasingly mature community is responding to the call for applications and is addressing important areas for research.

Dr. Raub indicated last week that it is a sign of maturity when the approval rate becomes relatively high. I think what we are seeing is a similar developing maturity within the nursing science community.

AGENCY FOR HEALTH CARE POLICY AND RESEARCH

Mr. NATCHER. What is your relationship to the new Agency for Health Care Policy and Research, Dr. Hinshaw?

Dr. HINSHAW. We have begun to relate to that agency on two fronts. First, we are interested in working with them on the effectiveness of care initiative. They are primarily looking, of course, at the effectiveness of care under medical treatment. However, nursing care and nursing treatment is very closely interdigitated with that, therefore we, too, have over time looked at effectiveness of care and patient outcome research in terms of nursing practice. We

will be talking with that agency about some cosponsored initiatives in the area of effectiveness of care and patient outcomes.

Second, we are currently cosponsoring a request for applications which has just been published this month on a rural health initiative with that agency and with the Division of Nursing. The focus of this research will be a community-based research and demonstration project investigating access to care for minority populations in a rural setting.

Mr. NATCHER. Dr. Hinshaw, will the new agency take the lead in nursing care outcomes research?

Dr. HINSHAW. No, I do not believe so. Their primary orientation has been toward medical effectiveness and medical care, and toward research programs on health services delivery. That is very different from the basic and clinical science which examines nursing interventions and patient outcomes, which is our mandate.

COLLABORATIVE INTRAMURAL RESEARCH PROGRAM

Mr. NATCHER. This year for the first time you are requesting staff for in-house research. How large do you expect your in-house effort to become in the next few years, Dr. Hinshaw?

Dr. HINSHAW. The National Advisory Council for Nursing Research has recommended a generous but careful development of the collaborative intramural research program.

We are very pleased with the program's initiation this year, but it is small. We have three members on staff currently assigned to the intramural program. We expect to increase that staff by two in the next year, and then every three to four years it will increase by an additional staff core of three to four individuals.

Mr. NATCHER. Will it be targeted mainly to AIDS?

Dr. HINSHAW. This initial program is targeted to AIDS, but that is because we have not received enough applications from the extramural community to investigate the physical care needs of AIDS patients in the latter stages of this disease.

However, in the future, with additional staff we would expect to elaborate that program to also work with the National Cancer Institute on symptom management and assessment, involving multiple types of symptoms, and later the third expansion is planned as a collaboration with the National Institute on Aging.

NCNR STAFFING

Mr. NATCHER. You are requesting an increase of seven full-time equivalents in 1991. Is this the end of the staffing buildup for your center?

Dr. HINSHAW. These staff are particularly important for the National Center because we do not as yet have in place a strong analysis and evaluation function, and we also are building the collaborative intramural research program.

I would not anticipate that this would be the end of the need for staff over time. As the programs grow, so will the staff, but the program growth will dictate the need for additional staff.

RESEARCH TRAINING GOALS

Mr. NATCHER. Are you meeting the research training goals set out for your institute several years ago?

Dr. HINSHAW. To date we have been able to meet those goals. In 1986 we started with 165 fellows and trainees who were supported in the entire field. At that point we were being advised by the National Academy of Sciences, in their recommendations for behavioral and biomedical personnel needs, that the field of nursing research needed by 1990 320 trainees annually. We put forth a plan in 1987 to reach a goal of 320, but by 1991 or 1992.

We have just completed the second step of the plan in FY 1989, and are thus far on target with the number of trainees to be supported. In 1989 there were 228. In 1990 we will support 257, and in 1991 we will need to straight-line the number and readjust that curve.

Mr. NATCHER. Mr. Pursell, I yield to you.

Mr. PURSELL. Thank you, Mr. Chairman.

Nice to have you back, Dr. Hinshaw. Thank you.

Dr. HINSHAW. Thank you.

OPPORTUNITIES FOR THE FUTURE

Mr. PURSELL. Tell me just as an overview how the nursing community nationally feels about the new Center and the hopes and opportunities for the future.

What is the general morale of the nursing community and interest?

Dr. HINSHAW. The level of excitement has remained very high. We see that clearly in the number of applications that we are receiving, and in the fact that we are attracting high-quality applications.

Regardless of the kind of program that we announce, we receive an unusual number of applications in response to the call, whether it is for a new research centers program, or an RFA for reducing frailty in the elderly.

I think also there has been a clear interest in the image building of the National Center—in the way it has boosted nurse investigators and faculty in many schools and universities.

NURSING SHORTAGE

Mr. PURSELL. With the major shortage of nurses throughout the country, it seems to me that the Center has an opportunity to sort of give nursing individuals who are in the profession a sort of a shot in the arm, of giving the institute a role in our National Center that would encourage the younger generation to get into nursing and stay in nursing and have an opportunity to do research and more comprehensive national goals.

Would that help attract, do you think, in the very broad sense?

Dr. HINSHAW. I think you stated the case very well. We have heard many anecdotal stories to that effect. The Tri-Council of national nursing organizations and the Ad Council are distributing an image campaign for nursing. The entire image campaign focuses on combining the caring and sensitive aspect of nursing with the intellectual and decision making aspect of nursing. The Center es-

pecially reinforces that intellectual and decision making aspect of nursing, as well as the caring research centers aspect.

Mr. PURSELL. We have the Center here, and we have a request for additional centers throughout the country, and you have approved two, is that correct?

Dr. HINSHAW. We currently have two specialized centers supported in the field and two exploratory centers.

Mr. PURSELL. Could you identify those for us?

Dr. HINSHAW. The two specialized centers are at the University of Washington, focusing on women's health issues, and at the University of Pennsylvania, with a research emphasis on advancing care in serious illness.

The two exploratory centers are at the University of Pittsburgh, with a focus on nursing practice problems in critical care illness, and at the University of Minnesota, specializing in long-term care of the elderly.

Mr. PURSELL. Where do you see the development of additional centers in the country? Would a decision be based on the quality and the merit of their requests, and certainly their history and their background, but would it be broad-based in terms of regional balance, or what criteria are you using to establish new centers?

Dr. HINSHAW. In this case the geography is not as compelling as the scientific merit, but we are concerned about regional balance.

There are many more schools in the nation which are able to compete for specialized centers and would compete well. Those are spread throughout all regions. To date we have made awards in Washington and in Pennsylvania for the specialized centers. Those are the large centers.

Mr. PURSELL. In response to minority needs, too, how does that fit into the development of the new centers?

Dr. HINSHAW. In several ways. All of the applications must include a minority core. They must tell us how they plan to either recruit minority investigators or minority research assistants who can then begin research training as part of the environment of the center core—although the centers don't support formal research training. Investigators must also outline research projects that will include minority populations.

PROFESSIONAL JUDGMENT BUDGET

Mr. PURSELL. With our request this year in dollars, obviously our institute, our National Center for Nursing Research is the smallest part of our organizational structure in the NIH. Can you take off your hat in the one place and tell me, tell us, where do you think it ought to be five, 10 years down the road?

Dr. HINSHAW. In my professional judgment, sir?

Mr. PURSELL. Yes, in your professional judgment.

Dr. HINSHAW. The professional judgment budget for FY 1991 is $50.3 million. That will give you some idea of the amount that it is clear we can spend, and spend well, in terms of quality research, research training and new centers program awards.

Mr. PURSELL. You have that kind of a demand placed on the center now around the country for applications?

Dr. HINSHAW. Absolutely, $50.3 million this year would only allow us to have a 25 percent award rate, which is the average award rate for all of NIH in FY 1991. That would be the first step in terms of some type of jump start. We would need to make a careful analysis to assess our needs five or ten years from now.

Mr. PURSELL. The restraint on dollars here makes it difficult for us to try to accommodate all the institutes. Well, I won't pursue that this morning.

Let me ask you one other question. The centers that are now in place that have been approved, are their agendas and their subject content the reason for selecting those centers? Do they fit into the long-term objective of the nursing community as part of the agenda of what issues are important in this nation in respect to the nursing community and its relationship to our health needs in this country?

Dr. HINSHAW. I believe the first two centers do so, sir. The difficulty is, with two centers established, there are many other research areas yet to be covered in terms of specialization.

Mr. PURSELL. How would you identify those other areas? What other areas are on in the priority list?

Dr. HINSHAW. I would identify them using the National Nursing Research Agenda, because they are the areas which the nursing community has recommended as the most important for nursing science to attack, and on which nursing research can have the most impact. Consequently we would encourage applications in low birthweight infancy, long-term care of the elderly, and possibly in the area of care of the AIDS patient. That last area will depend on how the intramural program develops, and what AIDS research proposals are available in the extramural setting.

Mr. PURSELL. And the dollars that are available to fund those?

Dr. HINSHAW. Absolutely.

Mr. PURSELL. Well, I toured a nursing research center last week, and I was very impressed with the excitement in the community at the university in response to the future of nursing.

I think you are off to an awfully good start. I see a lot of exciting opportunities in the future aside from dollars and constraints.

I hope that the committee can find ways and means to elevate our center here in order to give it national focus, which I think has been long, long overdue. I think our advancements at this point in the last few years, thanks to the committee and your leadership and others throughout the nursing community, that we are making some good progress, but I am not sure it is fast enough. I think the community out there is very mature and have been backed up, it has been backed up since a long time, and there has not been a channel here in which to creatively develop good nursing research in the component of the health community at large.

So I am very excited about your future and I wish you very well.

Thank you, Mr. Chairman.

Dr. HINSHAW. Thank you very much, sir.

Mr. NATCHER. Yes. Mr. Stokes.

RESEARCH OPPORTUNITIES FOR MINORITIES

Mr. STOKES. Thank you, Mr. Chairman.

Dr. Hinshaw, in your opening statement you mentioned that NCNR has implemented an initiative providing special research opportunities for minority faculty and students. I want to ask you about that initiative.

Before doing so, first tell us if you can, the extent to which minorities are represented in nursing research.

Dr. HINSHAW. In FY 1989, in terms of the nursing research portfolio, 8 percent of our dollars were invested in either research into minority health problems or in minority research training. That level is not as high as we would like it to be, and we understand—as does the rest of NIH—that it is an area that requires particular attention.

Mr. STOKES. Tell us about the minority research initiative.

Dr. HINSHAW. We are involved in the ongoing NIH initiatives to award minority supplements to our research project grants. We also have a special initiative to add minority trainees to the National Research Service Award Institutional Training Grants. There are 14 of those in the country. We have had approximately four individuals take advantage of this.

We are promoting this opportunity heavily, and the program directors in those 14 institutions are also recruiting minorities. We don't always know their ethnicity, sir, but we have increased from supporting three minority trainees in 1988 to over 12 in 1989. The numbers are low, but they do show our progress and the ability of the initiatives to help us develop this program.

LINKAGES WITH MINORITY NURSING SCHOOLS

Mr. STOKES. Last year, Doctor, you told us that you had been working with the Research Centers in Minority Institutions, the RCMI program, to encourage linkages with minority schools of nursing and minority nurses in research. What can you tell us about that program?

Dr. HINSHAW. In 1989 we awarded seven grants to investigators who are minority PIs and one research grant supplement to a minority co-investigator. That is about 5.4 percent of the principal investigators in our portfolio.

We are attempting to help more minority faculty who are in schools with RCMI programs to link with those programs. We would be more than willing to help support good peer-reviewed research and to help minority nurse scientists obtain that type of support.

MINORITY STAFF AT NCNR

Mr. STOKES. Doctor, tell us to what extent you have been able to recruit minorities into administrative positions at NCNR.

Dr. HINSHAW. We have one minority staff member who is now in a GS-13 position. A total of 6 of our employees in 1990 are minority colleagues equivalent to 18 percent of a staff of 34.

Mr. STOKES. All right.

In the record, provide for me, if you will, a breakdown of minority employees and each of the grade level positions that they hold.

Dr. HINSHAW. I would be delighted to, sir.

[The information follows:]

NATIONAL CENTER FOR NURSING RESEARCH

[Minority staff members]

Position title	Grade	Number
Executive secretary, review	14	1
Personnel management specialist	11	1
Administrative clerk	5	1
Secretary	5	2
Health scientist administrator	(1)	1
Total [2]		6

[1] Retired.
[2] Minority staff 18 percent of staff.

HEALTH AND BEHAVIOR RESEARCH

Mr. STOKES. What studies are being supported by the Center related to health and behavior? What percentage of the Center's budget is committed to health and behavior research?

Dr. HINSHAW. The nursing research makes a very strong emphasis on health and behavior research. Forty-seven percent of our present portfolio are studies in that area. Our behavioral research represented about 4.8 percent of the entire NIH budget of behavioral research in FY 1989, while the Center's whole budget was less than one half of 1 percent of the overall NIH budget.

The behavioral research includes, at one end of the spectrum, the kind of health promotion studies which focus on young adolescents, to help them understand high-risk behaviors and their effects on health, including smoking, drinking, and early sexual activity. Nursing interventions can then be utilized through school systems to help motivate young people not to begin those high-risk behaviors.

At the other end of the spectrum, our behavioral research includes recovery patterns from myocardial infarction and from hip fracture. We support a number of studies which will allow nurses to look at modifying patients' behavior, while regaining functional abilities following such surgical procedures or traumatic events.

LOW BIRTHWEIGHT INFANTS

Mr. STOKES. Dr. Hinshaw, one of your research priority areas is the prevention and care of low birthweight babies. What is the status of this research and what are we learning from it?

Dr. HINSHAW. We currently have a cluster of studies in this area. We know clearly that 6.8 percent of all live births are low birthweight infants, and that in the black population that proportion is doubled, which is I think is of particular concern to all of us.

The cluster of studies that we are currently supporting deals primarily with black and Hispanic populations. One study concerning nurse home visitation has found that if visiting nurses provide ongoing education, ongoing support and contact to young pregnant women, that is, the presence of an individual who cares about the health behaviors those young mothers undertake, it will not prevent low birthweight, but will be effective in raising the weight of the child at birth. The investigators have also seen fewer infections

following birth and fewer visits to emergency rooms, which gives some indication of less neglect or abuse.

CARE OF AIDS PATIENTS

Mr. STOKES. Doctor, another of your priorities for nursing research is the care of AIDS patients, their families, and partners. How is this research progressing?

Dr. HINSHAW. In this area of research in FY 1989, we supported $1.2 million. We have supported several studies which are over our AIDS allocation which have ramifications for other areas of research as well.

These studies tend to vary all the way from tracking pediatric AIDS infants of high-risk mothers, in which developmental patterns are examined, to studies of the kind of symptomatology which occurs at different stages in the HIV infection process, in order to help patients to both diagnose and manage those symptoms, such as fatigue, pain, and nausea.

Mr. STOKES. How many new awards would you be able to make in this area?

Dr. HINSHAW. There will be no new starts unless those awards have generalizability to other areas of research as well.

BIOETHICS AND CLINICAL PRACTICE

Mr. STOKES. In your opening remarks, you noted that NCNR has established a new program of research in bioethics and clinical practice. What are the most serious ethical issues confronting nurses today?

Dr. HINSHAW. I think the issue with this particular program—and the National Center is one of the few institutes with the legal mandate to carry forth this kind of research, as well as the Human Genome Center—we are particularly concerned with looking at clinical practice decisions that must be made, either by patients themselves or with their families, or by the health care providers.

Often these are decisions concerned with the withdrawal of life support equipment, the conflicts that occur around making that type of decision, and decisions about pursuing particular treatments which may have devastating side effects versus considering the quality of life issues. Those types of issues are very difficult to obtain data on, so this will be an empirically based program of study.

LONG-TERM CARE OF THE ELDERLY

Mr. STOKES. Doctor, what are some of the major research questions related to long-term care of the elderly?

Dr. HINSHAW. Long-term care of the elderly is a field in which we have several different research initiatives. We are particularly interested in targeting the caregiving issues involved with long-term care of the elderly, and we are investigating the parameters of these care-giving issues in the home as well as in institutional settings. In fact, today's Washington Post includes an article on page 12 of the Health Section exploring the many problems encountered by caregivers.

In the home, one of the major studies we are supporting concerns home care strategies designed to help individuals—Alzheimer's patients in particular—stay independent as long as possible.

Another of these studies is evaluating active stimulation training of the individuals who have Alzheimer's and are in the mild or moderate stages of that disease. Through a randomized trial, the investigator is comparing whether individuals who receive active cognitive stimulation versus passive cognitive stimulation can remain coherent and oriented for a longer period of time. The pilot work in this area was very positive and very promising.

Mr. STOKES. Do minorities have special needs in this area?

Dr. HINSHAW. Yes, there tends to be a higher rate of chronic illness, particularly due to cardiovascular illness, and in rural areas, there are special problems with lower socioeconomic status individuals—who may or may not be minority—having less access to health care delivery services.

Mr. STOKES. Is this one of the areas that you will be focusing heavily upon?

Dr. HINSHAW. Through the new initiative this year, we are putting $600,000 into research and demonstration projects, matched by the new Agency for Health Care Policy and Research and the Division of Nursing, to initiate projects in rural communities, particularly for minorities, to discover how we can best help them to access health care services.

Mr. STOKES. Thank you very much, Dr. Hinshaw.

Dr. HINSHAW. Thank you, Mr. Stokes.

Dr. Hinshaw, we want to thank you and your associates for appearing before our committee on behalf of your budget request for the fiscal year 1991. This has been a good hearing. Thank you very much.

Dr. HINSHAW. Thank you.

[The following questions were submitted to be answered for the record:]

Questions Submitted by the Subcommittee

RESEARCH TRAINING

Mr. Natcher. How much of your research training goes to predoctoral rather than postdoctoral researchers?

Dr. Hinshaw. In FY 1989, NCNR supported 187 predoctoral trainees at a cost of $2,479,000. This compares to 32 postdoctoral trainees under the NRSA program, at a cost of $968,000, as well as 9 career awards for $571,000. Therefore, 82 percent of the trainees in 1989 were predoctoral.

RESEARCH CENTERS

Mr. Natcher. Should the number of research centers be held constant until the Exploratory Centers become viable competitors for new center grants?

Dr. Hinshaw. Not necessarily. While the exploratory mechanism is designed to facilitate the development of future sites for specialized centers, many sites are able to develop their research capabilities independently, without the need for an exploratory center. We should make the opportunity available for these institutions to apply for and receive specialized center awards.

The National Advisory Council for Nursing Research recommends that the Specialized Centers increase to five in FY 1991, and that the Exploratory Centers increase to six. They further recommended that the number of centers increase again in 1993, to seven Specialized and eight Exploratory Centers.

CAREGIVING AND ALZHEIMER'S DISEASE

Mr. Natcher. How much funding are you allocating to research on Alzheimer's Disease and caregiving?

Dr. Hinshaw. In FY 1989, NCNR spent $1,854,000 toward research on Alzheimer's Disease and caregiving. We plan to spend $2,400,000 in FY 1990 and $3,400,000 in FY 1991.

COLLABORATIVE PROJECTS

Mr. Natcher. Provide a listing of research projects co-funded by NCNR and other Institutes which shows the dollar contribution of each.

Dr. Hinshaw. I have included the following table to illustrate all of NCNR's cofunding arrangements in 1989.

Collaborative Projects of the National Center for Nursing Research Awarded in FY 1989

Title and Mechanisms	Collaborating Agency	NCNR Amount	Collaborator's Amount
Cooperative Agreement: Models of Nursing Care: Differentiated Group Practice	Division of Nursing, Health Resources and Services Administration	176,586	170,675
Cooperative Agreement: Models of Nursing Care: Enhanced Professional Practice Model for Nursing	Division of Nursing, Health Resources and Services Administration	207,290	207,290
Research Project Grant: Study of Nurse Home Visitation for Mothers and Children	Office of Maternal and Child Health	218,117	453,406
Research Project Grant: Study of Nurse Home Visitation for Mothers and Children	Assistant Secretary for Planning and Evaluation	-----	150,000
Research Project Grant: Study of Nurse Home Visitation for Mothers and Children	Family Support Administration	-----	124,441
Research Project Grant: Preparation for Radiotherapy: Outcomes and Explanations	National Cancer Institute	44,628	44,627
Research Project Grant: Atrophy of Skeletal Muscle: Change in Tension Development	National Institute of Arthritis, Musculoskeletal & Skin Diseases	57,348	19,116

First Independent Research Support and Transition (FIRST) Award: A Nursing Intervention Lexicon & Taxonomy	National Library of Medicine	59,634	58,632
Research Project Grant: Nursing Model to Prevent Noise-Induced Hearing Loss	National Institute of Deafness and Communicative Disorders	44,474	44,474
Cooperative Agreement: Urinary Incontinence Clinical Trail	National Institute on Aging	116,495	116,495
MARC Visiting Scientists Fellowships: MARC Program	National Institute of Arthritis, Musculoskeletal & Skin Diseases	4,000	46,174
Specialized Center: Education Supplement to Alzheimer's Disease Research Center	National Institute on Aging	79,500	1,194,527
Specialized Center: Education Supplement to Alzheimer's Disease Research Center	National Institute on Aging	82,000	1,605,476
	Total of Collaborative Projects	1,090,072	4,235,333

NATIONAL NURSING RESEARCH AGENDA

Mr. Natcher. Identify the costs associated with the research priority plans developed to date.

Dr. Hinshaw. The first priority area, Low Birthweight: Mothers and Infants, was supported at a level of $0.8 million in FY 1989. We hope to increase significantly the research in this field through our initiative, building an additional $1.2 million in support over FY 1990 and FY 1991.

The second priority area, HIV Infection: Prevention and Care was supported at a level of $1.2 million in FY 1989. As we carry out this initiative, we hope to increase the support of nursing research in this field by about $1 million over 1990 and 1991.

PROFESSIONAL JUDGMENT BUDGET

Mr. Conte. In your professional judgment, what additional resources and money would you like to see allocated to the Center in FY 1991?

Dr. Hinshaw. In my professional judgment, now that the Center has in place solid foundations for substantial extramural and intramural programs, and the community has responded vigorously with numerous proposals for valuable research, the time is right for a major move forward. I will prioritize my opinions on the most vital needs of the Center by funding mechanisms:

1. $7,890,000 would allow restoration of noncompeting and competing research project grants to only a 7 percent reduction level, and would increase the number of competing awards to 57, equivalent to a 20 percent award rate.

2. $2,473,000 would permit the second step in development of the research centers program, by adding 3 specialized centers and 4 exploratory centers.

3. $631,000 would allow attainment of the third step of the training initiative, adding 17 trainees to the NRSA program and 6 research career awards, for a total of 280 trainees in 1991. This would include the initiation of the planned Nurse Scientist Award.

4. $433,000 added to the Collaborative Intramural Research Program would permit initiation of the next clinical protocol for nursing care research with HIV-positive patients in the NIH Clinical Center.

5. $3,255,000 in research project grants would bring the number of competing awards to 71, thereby attaining a 25 percent award rate. All of the awards would be reduced 7 percent.

6. $576,000 in Research Management and Support would allow staffing changes without loss of other services or delay of the national planning process to develop a National Nursing Research Agenda.

The needs of the NCNR could all be satisfied with a 1991 budget of $50,385,000.

Mr. Conte. What are your top priorities?

Dr. Hinshaw. My top priorities are definitely to mitigate the reductions on research project grants, to increase the number of competing awards to achieve at least a 25 percent award rate, to continue the vitally important research training initiative, and to take the second step in developing the research centers program.

NATIONAL NURSING RESEARCH AGENDA

Mr. Conte. I understand the first major research priorities have been developed from the Center's long-term planning endeavor -- the National Nursing Research Agenda. Could you describe the scientific priorities?

Dr. Hinshaw. Under the Center's long-term planning endeavor, the National Nursing Research Agenda (NNRA), seven broad priorities were initially identified by the NNRA Steering Committee. They are: HIV Infection: Prevention and Care; Low Birthweight: Mothers and Infants; Long-term Care for Older Adults; Symptom Management; Information Systems for Improving Nursing Care; Health Promotion in Children and Adolescents; and Technology Dependency Across the Lifespan. Each of these broad priorities will be refined by an interdisciplinary expert panel. The first five of these panels are presently operating, with the last two to be started in 1991.

One major area of interest of the HIV panel is preventing the transmission of the virus. Within this broad area, the panel is recommending studies describing the prevalence of high-risk behaviors, as well as studies to develop interventions to reduce such behaviors.

In the area of physiological aspects of nursing care for AIDS patients, interest focuses on studies of the management of distressing symptoms, such as fatigue and pain; as well as on the effectiveness of nursing interventions in slowing disease progression, improving the quality of life for patients, and encouraging adherence to therapeutic regimens.

In the psychosocial area of AIDS care, recommendations center on gaining greater understanding of psychosocial needs among special populations, such as caregivers of infected individuals and infected children.

And in the area of delivery of nursing services for care of AIDS patients, descriptive studies were recommended to identify the health care needs of various infected population groups, to evaluate the appropriateness and continuity of services available in various communities, and to identify effective methods of recruitment, retention, and support of nursing staff working with infected individuals.

The Low Birthweight panel has recommended research in four broad areas: preconception care, prenatal care, physical care of the infant, and caregiving and parenting.

High priority was given to prenatal care, with a recommendation for research to determine the effectiveness of the nurse-managed prenatal care programs in preventing low birthweight, including home visits, with special attention to women from rural and disadvantaged backgrounds.

Another area of major interest is in caregiving and parenting, in which recommendations were made to develop and test

a risk assessment system that depicts post-neonatal outcomes, as well as development and testing of post-discharge intervention strategies for low birthweight infants and families who are at risk for poor post-neonatal outcomes.

As part of preconception care, a high-priority recommendation was to develop, test, and determine the cost-effectiveness of nurse-managed preconception care, associated with the prevention of low birthweight, that optimizes health promoting behaviors of men and women in varying health care settings. NCNR plans to develop program announcements soliciting applications responsive to a number of the priorities proposed by these expert panels.

Mr. Conte. What program activities have been initiated for these scientific priorities?

Dr. Hinshaw. One of the priority areas identified for further study is methods of caring for low birthweight (LBW) infants in intensive care units. Physical care of these infants such as feeding, respiratory care, and skin care needs further basic and clinical research. NCNR, in collaboration with National Institute of Child Health and Human Development, published a program announcement to encourage research proposals to study optimum care practices for hospitalized LBW infants. NCNR is planning another program announcement to encourage research that focuses on the underlying causes of intrauterine growth retardation and premature labor in pregnant women.

Achieving successful prevention of AIDS and delivering optimum acute and long-term nursing care to persons with AIDS and their families are also priorities for the NCNR. NCNR is working with other PHS agencies to encourage studies that test the most effective interventions to ameliorate physiological and psychological symptoms. We have also joined other agencies in encouraging research that targets at-risk populations to test prevention strategies.

RESEARCH CENTERS

Mr. Conte. What is the progress of the new Centers program started by Congress in 1988?

Dr. Hinshaw. The new centers program was initiated in FY 1989 with the award of two Specialized Centers for Nursing Research and two Exploratory Centers for Nursing Research. The Specialized Centers are located at the University of Pennsylvania, with a research emphasis on Advancing Care in Serious Illness, and at the University of Washington, with a research emphasis on Women's Health Research. The Exploratory Centers are at the University of Minnesota, with an emphasis on Long-Term Care of the Elderly, and at the University of Pittsburgh, with an emphasis on Critical Care Nursing.

Mr. Conte. How many applications did you receive and how many did you fund?

Dr. Hinshaw. We received 11 applications for Specialized Centers, of which we awarded 2. We received 32 applications for Exploratory Centers, of which we also awarded 2.

Mr. Conte. What type of growth is needed for this new program?

Dr. Hinshaw. In the next 2 to 4 years, there will be a number of sites ready to compete for center awards. The National Advisory Council for Nursing Research recommends that the Specialized Centers increase to 5 in FY 1991, to 7 in FY 1993, and to 8 in FY 1995. The Council recommends that the Exploratory Centers increase to 6 in FY 1991, to 8 in FY 1993, and to 11 in FY 1995.

Mr. Conte. Please tell us about the Exploratory Centers and the research being supported by them.

Dr. Hinshaw. The Center for Nursing Research at the University of Minnesota focuses on Long Term Care of Elderly Populations. Pilot projects support research on assessment of factors related to falling, hospital discharge planning, aggressive behavior among the elderly, and issues related to informal and formal caregiving. The Exploratory Center at the University of Pittsburgh supports studies in critical care nursing such as safe techniques in mechanical ventilation, recovery following heart transplantation, and measures of family events and injury in children. Both Centers are forming strong multidisciplinary linkages within their respective institutions and utilizing existing research resources and expertise in building their programs of study.

RESEARCH TRAINING

Mr. Conte. The nursing research community has expressed the need for a strong initiative in research training for nurses. What have you done in this area and what remains to be done?

Dr. Hinshaw. In 1987, the NCNR defined a multi-year initiative in research training, with the ultimate goal being reach an annual level of 320 nursing research trainees supported, as recommended by the National Academy of Sciences in the 1985 report.

From a base of 171 trainees in 1987, the first step of the initiative was completed in FY 1988, with 194 trainees supported through the National Research Service Award fellowships and institutional training grants, as well as Academic Investigator Awards and Clinical Investigator Awards under the research career awards program. The second step of the initiative was completed in 1989, with 228 trainees supported. The third goal of 270 for 1990 has been adjusted to 257.

The Center has also emphasized the need for additional minority nurse scientist trainees through several special efforts. All of the institutional training grant institutions have been contacted about the availability of supplements for adding

minority nurse trainees to their programs. Two of the institutions succeeded in implementing this in FY 1989.

We also hope to begin a Nurse Scientist Program as another means of increasing the proportion of postdoctoral trainees. This will be similar to the Physician Scientist and Dental Scientist Programs of many of the other institutes. This will provide a special opportunity to build a cadre of clinical nurse researchers with a background of rigorous scientific training.

Mr. Conte. What postdoctoral training is NCNR supporting?

Dr. Hinshaw. Increased support of postdoctoral trainees has been a key part of NCNR's multi-year training initiative, in which we include research career awards as well as the traditional training grants. In FY 1989, 41 postdoctoral trainees were supported, representing 18 percent of the 228 total trainees that were supported that year. Nine of the trainees were on Academic Investigator Awards or Clinical Investigator Awards, 13 were postdoctoral fellows or senior fellows, and the remaining 19 were in postdoctoral training positions under institutional training awards.

As a continuation of the emphasis on increased postdoctoral training support, we estimate we will support 52 postdocs in FY 1990, amounting to 20 percent of the total training effort. Approximately the same number will be supported in FY 1991.

We also hope to begin a Nurse Scientist Program as another means of increasing the postdoctoral proportion of our trainees. This will be similar to the Physician Scientist and Dental Scientist Award programs of many of the other institutes.

COLLABORATIVE INTRAMURAL RESEARCH PROGRAM

Mr. Conte. What type of scientific opportunities are being pursued in the new Collaborative Intramural Program?

Dr. Hinshaw. The new Collaborative Intramural Research of the National Center for Nursing Research will initially focus on patient care issues pertaining to HIV infection. Its aim is to conduct research that will increase our understanding of, as well as develop nursing interventions for, the health problems that are particularly common among individuals with HIV infection, their families, and their caregivers.

Mr. Conte. What types of studies will you be conducting?

Dr. Hinshaw. The ultimate goal of this research program is to minimize dysfunction and suffering due to physical or psychosocial consequences of HIV infection and its medical treatment. Examples of these problems include, but are not limited to: unintentional weight loss, decreased appetite, or other nutritional disorders; fatigue; dementia, confusion, or other cognitive disorders; diarrhea; and mouth sores and oral discomfort. Common behavioral problems associated with HIV infection, such as anxiety, depression, loss and grieving, and

diminished quality of life are also within the purview of the NCNR's intramural research program.

Nurse scientists will characterize these problems as they occur in different stages of the disease and as they are effected by varying treatments. The investigators will formulate strategies for mitigating the effect of these symptoms on the patients, as well as on their families and caregivers. These interventions will then be published for use by nurses and other health care workers caring for HIV-infected individuals.

Mr. Conte. Do you plan to expand into other areas of nursing research outside of AIDS?

Dr. Hinshaw. Yes, we do. The opportunities for excellent nursing research studies within the clinical intramural programs at the NIH are numerous and promising. I believe that a logical extension of the intramural program, after the HIV research protocols are well established and sufficiently supported, will be to move into the field of nursing care for cancer patients. The similarity of some of the adverse side effects of cancer and its treatment to the adverse side effects of HIV treatment supports this sequence.

In the future, we would like to establish a program of intramural research regarding the special health care requirements of elderly populations, perhaps in collaboration with the National Institute on Aging. Nursing care needs of the elderly population are a steadily increasing challenge to the national health care system. The NCNR already supports a number of initiatives in segments of this field through its extramural programs, including research on the burdens of care of the elderly, the needs of patients in long-term care situations, special care strategies useful for working with patients who are incontinent, and ways to increase mobility and prevent injuries among the frail elderly. An intramural research program in this field would be a natural and valuable expansion of our current programs.

RURAL HEALTH CARE RESEARCH

Mr. Conte. Last year, Congress encouraged NCNR to enhance its research efforts in rural health care and allocated an additional $600,000 for this program. What is being done in this important field of research?

Dr. Hinshaw. Rural health care is an area of particular interest to NCNR. The staff have been active in evaluating the needs of those residing in rural areas, and have determined that the health of minority populations could be improved through the development and evaluation of community-based nursing practice models. These models will be targeted on the most vulnerable of minority persons, namely those over 65 years of age, childbearing women, adolescents at risk for early pregnancy, children and infants. In cooperation with the Division of Nursing, HRSA, and the new Agency for Health Care Policy and Research, we published a request for applications for research and demonstration project applications to be submitted on June 15, 1990. A total of

$1,500,000 is available from all three agencies, including the $600,000 provided to NCNR. This combined level of support will enable us to fund two or three proposals during FY 1990.

Mr. Conte. Do you expect the need for rural health care research will continue to increase?

Dr. Hinshaw. The research community's interest in our rural health request for applications (RFA) published in March 1990 is strong.. This effort is focused on the development and evaluation of community-based rural nursing practice models for minority populations. Also of concern to NCNR are underserved non-minority populations, such as developmentally disabled children in Appalachia; quality of patient care provided in institutional settings, such as nursing homes and small hospitals, and the access of rural populations to primary and tertiary care.

HEALTH AND BEHAVIOR RESEARCH

Mr. Conte. What studies are being done to look at health and behavior?

Dr. Hinshaw. The NCNR has a strong commitment to research on health and behavior. In FY 1989, $12,558,000 was spent on research and training in health and behavior. This area holds promise for improving health and preventing disease, since many of our present health concerns are the result of lifestyle choices and behaviors.

There are several types of research we support, including research to prevent and lower the risk of illness, and research on strategies to manage the symptoms of diseases and their treatment. One longitudinal study is examining risk-taking behaviors relative to overeating, drug use, early sexual behaviors and smoking in a group of rural adolescents. Identification of patterns of such behaviors in these areas will provide needed knowledge for interventions to motivate adolescents to maintain healthy behaviors.

Four studies are examining strategies to manage symptoms resulting from chemotherapy or radiotherapy used in treating cancer. Minimizing the effects of this type of treatment will allow patients to increase their functional level and ability to cope with their illness.

Mr. Conte. What percentage of the Center's budget is committed to health and behavior research?

Dr. Hinshaw. In FY 1989, the total of our research on health and behavior was $12,558,000, which represented 47 percent of our extramural funds. In FY 19910, we anticipate spending $14,300,000 in this field, and approximately the same in FY 1991.

MINORITY RESEARCH AND RESEARCH TRAINING

Mr. Conte. What program initiatives do you have for supporting minority related research and research training for minority colleagues?

Dr. Hinshaw. Minority research training remains a priority initiative for NCNR in FY 1990. Several strategies have been initiated. We are encouraging minority supplements to existing Institutional Research Training Awards and enforcing the requirement of minority recruitment plans for any new awards. NCNR has encouraged minority faculty and student supplements to existing research awards and provided assistance in linking people with similar research interests. NCNR requires the Specialized Centers to include a minority recruitment component to encourage training in research intensive environments. We have held workshops on funding opportunities in the past, targeting institutions with large minority populations, and we plan to provide this kind of consultation in the future. NCNR will reconvene an Ad Hoc Advisory Committee on Minority Training to provide advice on future initiatives.

NCNR is currently funding several studies that address health risk factors in minority populations. Over $2.1 million was spent in FY 1989 on research projects that focus on minority health. The priority areas identified for targeted efforts, Prevention and Care of Low Birthweight Infants, HIV Infection: Prevention and Care, and Long-Term Care of Older People all have major implications for minority populations.

COMPETING RESEARCH PROJECT GRANTS

Mr. Conte. Dr. Hinshaw, how many competing research awards do you plan to fund in FY 1991?

Dr. Hinshaw. We expect to award 33 competing research project grants in FY 1991.

Mr. Conte. How does this compare to the number of competing awards made in the past several years?

Dr. Hinshaw. It is, on the average, 33 percent lower than we have awarded in previous years. In the current year, FY 1990, we estimate we will award 45 competing grants. In 1989, the last complete year, the NCNR awarded 50 competing grants. In 1988, the NCNR awarded 52 competing projects, and in 1987, 48 competing grants were awarded.

AWARD RATES

Mr. Conte. What will be the projected award rate for NCNR in FY 1991?

Dr. Hinshaw. The projected award rate in FY 1991 is 12 percent.

Mr. Conte. How does this compare to the predicted NIH award rate?

Dr. Hinshaw. The NIH-wide award rate projected for FY 1991 is 25 percent.

Mr. Conte. How much additional money is needed to achieve a 25 percent award rate in FY 1991?

Dr. Hinshaw. It would take an additional $10.3 million over the President's request for NCNR to achieve a 25 percent award rate in FY 1991. This would equate to awarding 71 competing awards, 38 more than are in the request.

NEGOTIATION OF RESEARCH PROJECT GRANTS

Mr. Conte. What is the anticipated downward negotiation rate of both competing and noncompeting awards in FY 1991 as compared to FY 1990 and 1989?

Dr. Hinshaw. The estimated downward negotiation rate in FY 1991 is 17.8 percent for noncompeting and 16.5 percent for competing research project grants. In FY 1990, the apparent rates of negotiation are 11.8 percent on noncompeting and 12.3 percent on competing. In 1989, our downward negotiation rate was 11.1 percent for noncompeting and 10 percent for competing.

Mr. Conte. If this is greater in 1991, why aren't you funding more, rather than fewer, competing RPGs?

Dr. Hinshaw. The NCNR has experienced a significant growth in the average size of its grants, as have other NIH components. Another consequence of being a young program, with only a few years of existence, is that we have been supporting a rapidly growing number of outstanding scientists who are now receiving noncompeting continuations. As a result, we are using an increasing proportion of our research project grant funds to support the noncompeting portion of the portfolio.

RESEARCH MANAGEMENT AND SUPPORT

Mr. Conte. Dr. Hinshaw, there is very little increase in the proposed budget for research management and support. With the center growing, don't you have additional needs for FTE's, supplies, and equipment?

Dr. Hinshaw. Yes, we do anticipate additional needs in the Research Management and Support activity. As we have progressed through the early growth stages of the NCNR, we have found that the number of research grant applications received has increased dramatically from 160 in 1987, NCNR's first full year at NIH, to 264 in 1989, an increase of 65 percent over 2 years. As NCNR has grown over the past 4 years, we have recognized, and responded to the need to develop more new programs, program announcements, and requests for applications each year to better serve the needs of the nursing research community. As our programs continue to grow and expand, and as we add more structure to the Center in order to

conform to the organizational and administrative requirements associated with being part of the NIH environment, we anticipate we will have additional needs for FTE's, supplies, and equipment.

Mr. Conte. Can you continue to effectively service the community with the dollars requested in RMS?

Dr. Hinshaw. We will do everything possible to ensure that we continue to effectively service the needs of the nursing research community in 1991. As the programs of the NCNR continue to grow, so do the costs associated with managing these programs. The 1991 request for the Research Management and Support (RMS) activity is $3,082,000, an increase of $283,000 over the comparable 1990 Appropriation. Certain items in the RMS activity have mandatory cost increases over which we have no control, such as within grade pay increases, general pay raises, or payments for centrally furnished services. In 1991, the sum of all of these "mandatory" increases totals $346,000. In addition, the 1991 budget proposes an increase of 5 FTEs in the RMS activity in 1991. With the $283,000 increase proposed in the budget, we will only be able to support a portion of the increased mandatory costs in 1991. The remaining portion of the increased mandatory costs, as well as the salary costs associated with the five additional FTE's, will be absorbed by delaying program expansions, halting the initiation of new programs, and deferring the purchase of anything other than critical equipment and supplies until sufficient funds are available in the budget. We will, however, do everything possible to minimize disruption to the nursing research community, as we continue to maintain high quality service.

LOW BIRTHWEIGHT INFANTS

Mr. Conte. One of the most important of NCNR's research priorities is the prevention and care of low birthweight babies. This is central to our effort to reduce the rate of infant mortality. What is the status of research in this area?

Dr. Hinshaw. The NCNR has been active with the research priority of the prevention and care of low birthweight infants. An interdisciplinary priority expert panel has defined the state of the science in this field. One outcome of the panel is a Program Announcement related to the physical care of low birthweight infants in the hospital. This is co-sponsored with the National Institute of Child Health and Human Development and has received excellent response from the community. A second Program Announcement is being developed related to the prevention of low birthweight infants.

The research on low birthweight infants focuses on four areas: preconception health care, the prevention of low birthweight through the prevention of premature labor and the prevention of intrauterine growth retardation, nursing care of the low birthweight infant in the neonatal intensive care unit, and parental caregiving for the low birthweight infant after

discharge. This research is conducted by nurse scientists in collaboration with scientists of other disciplines.

Studies of the care of the low birthweight infant include a test of a nursing intervention to facilitate the interaction and understanding of the mother for her low birthweight infant. Another investigator has examined the response of the low birthweight infant to touch, and a third nurse scientist is determining the responses of the low birthweight infant and mother to breastfeeding.

Mr. Conte. What are we learning from this research on low birthweight?

Dr. Hinshaw. From this research we are learning more about women's behaviors and factors related to the increased risk for giving birth to low birthweight infants, such as smoking, alcohol, substance abuse, and stress. Studies related to the prevention of low birthweight include the determination of the reasons women seek or do not seek adequate prenatal care, and the testing of a social support intervention for black women in relation to the outcomes of the pregnancy. Through our current research we are also beginning to know more about the etiology of premature labor and intrauterine growth retardation. As we learn more about the factors affecting low birthweight infants, there is increasing need for multifactorial, interdisciplinary studies to examine the interaction of the biomolecular, physiological, behavioral, and system factors affecting the prevention of low birthweight. A significant area for research is intervention studies for the prevention of pregnancies in adolescents and studies to support changes in maternal behaviors to prevent premature labor and intrauterine growth retardation.

NCNR funded several studies related to low birthweight infants' responses to care activities such as handling, feeding, and therapy procedures. One investigator is examining the relationship between temperature and the ability of the low birthweight infant to achieve sleep - awake states. Also included are studies of the low birthweight infants' ability to demonstrate their readiness for feeding, and to determine the energy expenditure for feeding.

We are learning the significance of care procedures for the low birthweight infant and that the infant's responses to care procedures are influenced by the behavior and organizational state of the infant. Clinical studies to further test the care procedures and the responses of the infant are necessary to reduce infant morbidity. We know from nursing research that low birthweight infants may have ongoing problems including some behavioral or learning problems not apparent until the child enters school. We need to continue to study these children over time and to study the care that they receive in the neonatal units and the interventions through early childhood. Another study showed that follow-up of the low birthweight infant and mother by a nurse specialist can result in earlier and safe discharge of the infant.

AIDS RESEARCH

Mr. Conte. Another important area of nursing research is the care of AIDS patients and their families. What progress has been made in this area?

Dr. Hinshaw. Much of the care provided to people with AIDS takes place in the home, either in the form of self-care or by friends and relatives. NCNR is funding one project that is developing and testing a computer link system that will connect people in their homes with the latest information about HIV and community services, as well as access to experienced nurses who will review and respond to computer messages daily. The network will provide a link not only with professional health care providers, but also with peers, thereby potentially helping to combat the problem of social isolation among patients and their care partners. Network users will be able to send and receive messages in complete privacy and anonymity.

Mr. Conte. How much funding are you requesting to continue your projects in AIDS research?

Dr. Hinshaw. The NCNR request for FY 1991 includes $1,148,000 for AIDS research.

Mr. Conte. Are you planning to make any new awards in FY 1991 in AIDS?

Dr. Hinshaw. The FY 1991 request will maintain those AIDS projects currently underway, and will not accommodate the awarding of any new projects.

CAREGIVING AND ALZHEIMER'S DISEASE

Mr. Conte. What research are you supporting on the caregiving of patients suffering from Alzheimer's Disease and the other dementias?

Dr. Hinshaw. The progressive dementia and physical debilitation of Alzheimer's Disease (AD) make it a challenge for families who are providing care to their loved ones. Many family caregivers seek information about appropriate health services for their family member and nursing consultation to assist them in the difficult tasks related to caregiving in the home. Knowledge of the scientific basis for caregiving strategies is crucial to professional nursing practice in this area.

The NCNR is currently funding research studies and research training relative to caregiving of patients with Alzheimer's Disease totalling $1,853,000. Some of these are examining delivery systems, such as the study at the University of Iowa that is identifying the effectiveness of special care units for AD patients, and the study at the University of Pennsylvania that is testing the effect of discharge planning procedures on hospitalized elderly persons, including patients with AD and related disorders. Results from these studies will provide needed

information on how patients can utilize existing health care services.

Research is also being supported to identify and test strategies used by family caregivers in the home. A study at the University of San Diego is examining the effect of family-based intervention on the cognitive stimulation of AD patients, on the well-being of the caregiver and on the interaction between the patient and the caregiver. The needs of the caregiver, as well as the effectiveness of their caregiving behaviors, must be addressed if the caregiver is to preserve his or her own health, in order to provide needed care to the person with Alzheimer's disease.

Mr. Conte. How much funding are you requesting for research to study the burdens of caregivers in FY 1991?

Dr. Hinshaw. Our estimate of the research in caregiving and Alzheimer's Disease which the NCNR will support in FY 1991 is $3.4 million.

Mr. Conte. What was the response in research applications in FY 1990?

Dr. Hinshaw. To encourage additional applications for 1990, the NCNR published two program announcements in FY 1989 related to Alzheimer's Disease and caregiving: one for research projects and one for research training. While it is too early to report on the actual number of applications in response to these announcements in 1990, we are pleased to report a number of enthusiastic phone calls seeking further information about these announcements. In FY 1989, the Center received 11 unsolicited research project grant applications related to Alzheimer's Disease and caregiving, totaling $2.5 million.

RESEARCH TRAINING

Mr. Stokes. Your goal in the area of research training for FY 1990 was 270 trainees, but you have had to adjust this downward for budget reasons. What was your original goal regarding the number of trainees for FY 1991?

Dr. Hinshaw. Within the original plan for the NCNR multi-year research training initiative, 1990 was scheduled to be the fourth and final step. This would have brought the annual total of trainees supported to 320, thereby achieving the level recommended by the National Academy of Sciences in their 1985 report.

Mr. Stokes. How does this compare with the number that can be supported under the President's Budget?

Dr. Hinshaw. The request we have made for FY 1991 will maintain the same level of training the NCNR has in FY 1990 -- 257 trainees, including research career awards.

RESEARCH CENTERS

Mr. Stokes. You stated that last year NCNR awarded its first four center grants. How many applications did you receive?

Dr. Hinshaw. The response from the nursing science community to announcement of the first centers of excellence in nursing science was very enthusiastic. We received 11 applications for the specialized centers, of which we awarded two. For the exploratory centers, we received 32 applications, of which we awarded two.

Mr. Stokes. The FY 1991 request for centers is for level funding at $1.235 million. This is over $200 thousand less than they were supported in FY 1989. At the President's request, what level of downward negotiation would be required to maintain 4 centers?

Dr. Hinshaw. In order to maintain the four centers, our downward negotiation rate will be 9.3 percent.

PAYLINES AND AWARD RATES

Mr. Early. To what percentile payline will you fund under your FY 91 request, and how does this compare to FY 90 and FY 89?

Dr. Hinshaw. The NCNR will pay to a percentile payline of 11 with the competing research project grant funds in the 1991 request. This compares to an estimated percentile payline of 18 in FY 1990, and an actual percentile payline of 26 in FY 1989.

Mr. Early. What percentage of approved grants will be funded under your FY 91 request and how does this compare with FY 90 and FY 89?

Dr. Hinshaw. The NCNR will have an award rate of 12 percent in FY 1991. This compares to an estimated award rate of 19 percent in FY 1990, and an actual award rate of 25 percent in FY 1989.

NEGOTIATION OF RESEARCH PROJECT GRANTS

Mr. Early. To what extent will there be downward negotiations in competing and noncompeting research project grants at the center?

Dr. Hinshaw. The estimated downward negotiation rate in FY 1991 is 17.8 percent on noncompeting and 16.5 percent on competing project grants. In FY 1990, the apparent rates of negotiation are 11.8 percent on noncompeting and 12.3 percent on competing. In practice, we are downward negotiating each grant by 12 percent in 1990. In 1989, we downward negotiated noncompeting grants by 11.1 percent and competing grants by 10 percent.

Mr. Early. Since the center is relatively new, what impact do you think another year of significant reductions will have, particularly in terms of building momentum?

Dr. Hinshaw. The downward negotiations are always difficult for the investigators to accommodate, especially when they reach a size of 12 percent or more. Many of our investigators now have had two or three years of reductions, and report that the pace of the projects must be slowed.

RESEARCH CENTERS

Mr. Early. The NCNR has established two specialized centers and two exploratory centers. What is the purpose of establishing exploratory centers grants, and how does this program differ from the specialized centers program?

Dr. Hinshaw. The exploratory grant mechanism encourages institutions in which a limited amount of research is ongoing to develop their scientific endeavors further. Toward that end, the center award supports pilot and feasibility studies, to encourage the building of a base for larger research studies. There are schools of nursing in the country that are just beginning to establish active research efforts, and could benefit from this

mechanism. In addition to the goal of assisting the development of greater research in each institution, the completion of an exploratory grant may prepare the institution and the investigators to compete for a specialized center grant.

The specialized center mechanism, on the other hand, is oriented to the institutions in which there is an existing cadre of experienced researchers ready to build on an existing base of research activity. The aim of this award is to encourage further depth of research in a specified area of science, and to achieve a greater productivity than would be possible with individual projects and training awards.

Mr. Early. How many applications were received for each?

Dr. Hinshaw. We received 11 applications for Specialized Centers, of which we awarded two. We received 32 applications for Exploratory Centers, f which we also awarded two.

Mr. Early. What is the average award for specialized centers?

Dr. Hinshaw. The average specialized center award size in FY 1989 was $545,000 in total costs. As a matter of policy, these awards were limited to $350,000 in direct costs for the first year.

Mr. Early. What is the average award for exploratory center grants?

Dr. Hinshaw. The average exploratory center award size in FY 1989 was $107,000 in total costs. As a matter of policy, these awards were limited to $75,000 in direct costs for the first year.

Mr. Early. Will there be downward negotiations in the centers program in FY 91 and, if so, how large will this reduction be?

Dr. Hinshaw. We expect to downward negotiate the awards for the specialized centers by about 15 percent in FY 1991. The exploratory centers will not be subject to downward negotiations, because of their modest size.

RESEARCH TRAINING

Mr. Early. In research training, a particular area of emphasis for the center was enlarging the pool of postdoctoral trainees. How many postdoctoral training awards were made in FY 89, and how many are planned for FY 90 and FY 91?

Dr. Hinshaw. In FY 1989, the NCNR supported a total of 41 postdoctoral trainees. There were 32 postdoctoral trainees under the National Research Service Award (NRSA) program and nine recipients of research career awards. In FY 1990, we estimate that we will support 52 postdoctoral trainees, consisting of 40 under the NRSA program and 12 through research career awards, and the same number in FY 1991.

Mr. Early. How would you assess progress in this area?

Dr. Hinshaw. I am pleased with the Center's success in raising the postdoctoral proportion of trainees. Because of the nature of nursing training, preparation of nurses for a PhD constitutes preparation for a second degree. The Center's training programs began primarily as a predoctoral program, with only eight percent postdoctoral trainees in 1986. One of the aims of our research training initiative has been to continue to increase the proportion of postdoctoral trainees, in order to increase the intensity of research training for our young investigators. Toward that end, we succeeded in raising the proportion of postdocs in the program to 18 percent in FY 1989, and we hope to achieve a 20 percent proportion in FY 1990 and FY 1991.

We also hope to begin a Nurse Scientist Program as another means of increasing the proportion of postdoctoral trainees. This will be similar to the Physician Scientist and Dental Scientist Programs of many of the other institutes. This will provide a special opportunity to build a cadre of clinical nurse researchers with a background of rigorous scientific training.

INNOVATIVE NURSING CARE DELIVERY MODELS

Mr. Early. Two innovative nursing care delivery models are being supported by the NCNR and the Health Resources and Services Administration (HRSA). Tell us a little about these projects. Is HRSA providing funds for these projects?

Dr. Hinshaw. Mr. Early, I am pleased to tell you about the innovative nursing practice models that NCNR and the Division of Nursing, HRSA are jointly supporting. Two Cooperative Agreement awards for the demonstration and evaluation of innovative nursing practice models for hospitals in urban and rural settings were funded in 1988. As these are five-year projects, I anticipate that results will not be available until 1993.

One of these awards, to the University of Arizona, is supporting the testing of the effect of a nursing unit-based Differentiated Group Professional Practice Model (DGPP) on professional practice, quality of care and cost outcomes, patient satisfaction, nurse satisfaction, and nursing resources. The DGPP model combines the components of group governance with shared clinical and administrative decision making, differentiated care delivery where the clinical nursing role is determined by the nurse's level of competence, and changed organizational culture to foster shared clinical and professional values. The effects of the DGPP model are being tested using a total of 7 urban and rural hospitals in Arizona.

The other project, awarded to the University of Rochester, is evaluating the Enhanced Professional Practice Model (EPP) to determine the effect of increased control over practice on quality of care delivery and patient outcomes, nurse satisfaction, and cost impact of the model. The EPP model combines components of staff nurse control over practice and resources at the unit level,

increased participation in decision making, flexible work hours, interdisciplinary care planning, and discharge planning that facilitates continuity of care through follow up at home. The effects of the EPP model are being tested using a total of 5 urban and rural hospitals.

CLINICAL TRIALS

Mr. Early. Does the center plan to support any clinical trials in either FY 90 or FY 91? If so, tell us a little about these trials.

Dr. Hinshaw. The National Center for Nursing Research is not currently supporting any clinical trials, and there are no plans for doing so in FY 1991.

AIDS RESEARCH

Mr. Early. Would you highlight your program plans for FY 90 and FY 91 in the area of AIDS research?

Dr. Hinshaw. Program plans for FY 1990 and FY 1991 in the area of AIDS research were recommended by a multidisciplinary group of scientists as part of the development of a National Nursing Research Agenda. The areas targeted for development include testing nursing interventions to prevent or ameliorate physiological symptoms such as pain, fatigue and unintentional weight loss. Issues related to the quality of life will also be addressed. This effort will include both the extramural programs and the new Collaborative Intramural Research Program.

NCNR is also working with other Federal Agencies in encouraging behavioral research in support of AIDS prevention. The Agency for International Development, the National Institute on Aging, and the National Institute of Child Health and Human Development, along with the NCNR, are seeking applications on basic research that will provide information concerning high-risk behaviors and behavioral changes related to the transmission of HIV throughout a person's lifetime.

Mr. Early. Is the NCNR AIDS program supporting any research in the area of AIDS/HIV and children (not infants) and adolescents?

Dr. Hinshaw. One study that NCNR is supporting aims to provide the knowledge base required for nurses and other health care providers to develop individualized effective educational programs regarding safe sexual behavior for adolescents. The investigators are surveying college students in three universities within a major biracial metropolitan area. They will also test aspects of the Health Belief Model in adolescents.

ALZHEIMER'S DISEASE RESEARCH CENTER SUPPLEMENTS

Mr. Early. The NCNR has awarded supplemental grants to NIA's Alzheimer's Disease Research Centers to fund educational programs for providing care to AD patients. What does this effort entail? What do you hope to accomplish?

Dr. Hinshaw. The NCNR awarded two supplemental grants totaling $161,500 to two Alzheimer's Disease Research Centers (ADRCs) in FY 1989. One award was to the ADRC at Johns Hopkins University in Baltimore, Maryland, to develop a teaching module that will assist health care providers in the appropriate use and monitoring of psychotropic drugs commonly used to treat persons with Alzheimer's Disease (AD). These materials will include a videotape, a training manual, recommendations for its use, and plans for distribution. It will contain special nursing considerations such as the principles of pharmacokinetics in the elderly, classifications of psychoactive drugs, contraindications for drug usage, side effects, and methods for monitoring and documenting relevant information for the physician and the family. The content of the teaching module will synthesize scientific information from many disciplines such as nutrition, clinical laboratory science, medicine, psychiatry and nursing. The videotape will illustrate common side effects of the drugs, and the nursing assessment of patients with problems due to drugs being used. By providing nurses and other health care providers with current information on the management of drug therapy, these teaching modules will contribute to better care for persons with AD.

The second supplemental award was made to the ADRC at Washington University in St.Louis, Missouri, to develop an educational package focusing on cognitive assessment and use of assessment data in the management of home health care clients. Since persons with AD are often unable to respond to caregivers with the usual verbal responses, due to cognitive loss from the disease, alternative methods of assessing these patients are needed. This project will provide videotaped vignettes of problem situations in the home setting, and the practical application of assessment techniques appropriate to the situation. Companion written materials will be developed to stimulate and focus discussion not only about the assessment techniques but also about the use of information gathered and the development of treatment plans. This will enable nurses and other home health care professionals to perform cognitive assessments skillfully and consistently, and to generate better care plans based on improved assessment.

PROFESSIONAL JUDGMENT BUDGET

Mr. Early. Doctor Hinshaw, if there were an increase over your FY 91 budget request, how would you use these additional funds? What would you priorities be?

Dr. Hinshaw. The Center has in place solid foundations for extramural and intramural programs, and the community has responded vigorously with numerous proposals for valuable research. The time is right for a major move forward. I will prioritize by funding mechanisms the best use of additional funds:

1. I would restore noncompeting and competing research project grants to only a 7 percent downward negotiation level, and would increase the number of competing awards to 57, equivalent to a 20 percent award rate.

2. I would proceed to the second step in development of the research centers program, adding 3 specialized centers and 4 exploratory centers.

3. I would proceed to the third step of the training initiative, adding 17 trainees to the NRSA program and 6 research career awards, for a total of 280 trainees in 1991. This would include the initiation of the planned Nurse Scientist Award.

4. I would add to the Collaborative Intramural Research Program to permit initiation of the next clinical protocol for nursing care research with HIV-positive patients in the NIH Clinical Center.

5. I would add another 14 research project grants, bringing the number of competing awards to 71, thereby attaining a 25 percent award rate.

6. I would increase the Center's staff to 47.

NURSING SHORTAGE

Mr. Early. We continue to hear a great deal about the shortage of nurses. Have we learned anything new within the past year?

Dr. Hinshaw. The increasing demand for nurses in this country remains a great concern, especially given the problem of decreased enrollments in nursing schools during the past several years. However, the latest study from the American Association for Colleges of Nursing suggests that enrollments in the baccalaureate programs of nursing may be turning around and have actually increased approximately 5 percent.

The NCNR is supporting a cluster of studies investigating the factors in clinical settings which will enhance the retention of nurses within their positions. These factors include shared governance, contract units and supervisory styles of leadership which facilitate the autonomy and professional decision making ability of the nurse. These studies on Innovative Practice Models for Nursing Care Delivery are in progress, and will be continued through FY 1993.

Mr. Early. What research will the Center be supporting in this area in FY 90 and FY 91?

Dr. Hinshaw. In FY 1989, the NCNR supported six studies for a total of $1,297,000 in the area of nursing shortage and its effect on the quality of care. In FY 1990 and FY 1991, approximately $1,800,000 is planned for studies in this area. The projects include the study of innovative practice models for delivering nursing care and their relationship to patient and staff outcomes. Other investigations focus on: a contract hospital unit model for reorganizing nursing resources and enhancing retention; and on the relationships among nurse managers, nursing retention and patient outcomes.

RESEARCH SUPPORT BY BRANCH

Mr. Early. How are your FY 90 funds and FY 91 request allocated among the three principal areas of research at the NCNR?

Dr. Hinshaw. We do not strictly allocate the funds by Branch. Instead, we respond to whatever area the best applications are in, and fund them. The result in FY 1989 was that the Acute and Chronic Diseases program supported grants and training awards representing 43 percent of the Center's extramural funds. The Health Promotion and Disease Prevention Branch's awards represented 35 percent of the extramural funds, and the Nursing Systems Branch represented 22 percent of the funds. I believe that these proportions will be similar in FY 1990 and FY 1991.

INTRA-AGENCY AGREEMENTS

Mr. Early. The justification indicates that the Center will fund 3 R & D contracts in FY 90 and 4 in FY 91. What activities will be supported with these contracts?

Dr. Hinshaw. The money on the contract line is used to support intra-agency agreements each year for collaborative efforts with other Federal agencies. For example, in FY 1989, the NCNR transferred $100,000 to the Division of Nursing (DN) in the Health Resources and Services Administration for support of a study of the supply of nurse anesthetists in the Nation, and the demand of the health care system for them. In FY 1990, the bulk of the money, $272,000, has been transferred to DN for the administrative support costs of the new Commission on Nursing Shortage.

BREAST AND CERVICAL CANCER

Mr. Early. Prevention and early detection of cancer, such as breast cancer, is a research interest of the NCNR. The Centers for Disease Control will be launching a breast and cervical cancer initiative. One of the elements of this program is encouraging screening and early detection and treatment. Does the NCNR plan any cooperative or collaborative efforts with the Centers for Disease Control in this area?

Dr. Hinshaw. The NCNR is eager to cooperate and collaborate with all federal agencies in the quest to prevent and detect cancers through scientific inquiry. However the NCNR does not have any collaborative efforts planned with the Centers for Disease Control.

Mr. Early. What research activities will the NCNR be supporting in the area of breast and cervical cancer in FY 90 and FY 91?

Dr. Hinshaw. NCNR is currently funding 24 investigators who are studying research questions in the area of cancer. Seven of these research grants are studying breast cancer, and four are studying patients with gynecological cancers, including cervical

and uterine cancers. Examples of breast and gynecological cancer studies currently funded by NCNR include: testing interventions to combat nausea and vomiting as side effects of radiation treatment; description and testing of interventions to increase coping and hope of breast and gynecological cancer patients and family members during diagnosis, treatment, and follow-up visits; and testing of interventions to increase energy levels of breast and gynecological cancer patients by increasing the body's ability to use oxygen effectively, so that activities of daily living can be maintained.

AGENCY FOR HEALTH CARE POLICY AND RESEARCH

Mr. Early. A major area of emphasis in your clinical research program appears to be patient outcomes. Can you tell us how NCNR's activities differ from those of the newly created AHCPR?

Dr. Hinshaw. The basic and clinical research needed to guide nursing practice focuses on the explanatory mechanisms needed to understand nursing care issues and the relationships among nursing interventions and patient outcomes. Those are the NCNR's interest. The new agency's research activities are focused in two areas: the Medical Care Effectiveness Treatment Program and the Health Services Research Program. The emphasis of the first program is primarily on the evaluation of medical care effectiveness. While nursing care effectiveness will be considered in that program in relationship to medical care treatment and patient outcomes, most of the research will be directed to care by physicians.

Mr. Early. Will the new agency be conducting research and studies that the NCNR is capable of doing?

Dr. Hinshaw. Since the scientific mission of the two agencies differs, only a limited number of the AHCPR's studies could be duplicative with those supported by NCNR. These include studies focused on health care delivery systems and their influence on nursing staff functioning. In the areas where there is possible overlap in programs, the agency and NCNR staff plan to work collaboratively and cosponsor research initiatives.

BIOETHICS AND CLINICAL PRACTICE RESEARCH

Mr. Early. What is the rationale for establishing an extramural program in bioethics and clinical practice research?

Dr. Hinshaw. The Bioethics and Clinical Practice Research Program was initiated after considerable thought and discussion with our National Advisory Council on Nursing Research. Patients are frequently placed in positions of making difficult and conflicting decisions for themselves, as are family members who must make similar decisions for them, when the patients are unable to do so for themselves. It is generally believed that the wishes of patients about the use of certain treatments for their disease, about continuing treatment beyond a certain point, and about the use of extraordinary measures to sustain their lives should be

given appropriate consideration by health professionals when decisions are made in these areas. Evidence indicates that patients' wishes are not consistently considered in these matters.

NCNR staff and advisory council members examined the existing research base on ethical issues in clinical practice, and found that most of the previous research was conducted from the philosophical perspective. Most of the findings were therefore not readily applicable outside the unique situation being examined. In addition, it became increasingly clear that the major emphasis initially should be on issues that arise during clinical decision making.

Two initiatives have been undertaken -- a small grants program and a research training program focused on bioethics and clinical decision making. The small grants program is designed to encourage qualified researchers and multidisciplinary research teams to submit small-scale studies and pilot projects that can assist in seeding this area of inquiry so that larger studies can be undertaken later based on this development work. The research training program recognizes that few researchers are prepared to carry out empirically based bioethical studies in clinical practice, particularly in clinical decision making, and is designed to facilitate entry of newly developing investigators, and senior scientists who wish to refocus their research direction, into bioethics research.

WOMEN'S HEALTH RESEARCH

Mr. Early. Women's health is the focal point for one of NCNR's centers. Do you plan any collaborative efforts with the National Institute of Child Health and Human Development?

Dr. Hinshaw. NCNR research grants investigate women's health issues concerning reproductive health, recovery from myocardial infarctions, bone density in midlife women, and problems with urinary incontinence in women. Research grants on women's reproductive health may be done in collaboration with NICHD. We plan to work with NICHD in encouraging applications that address factors related to premature labor and intrauterine growth retardation in FY 1990 and FY 1991.

HIV EXPOSURE RISK FOR NURSES

Mr. Dwyer. The AIDS program conducted by the NCNR supports basic and clinical research on the physical, psychosocial, and ethical problems central to the prevention of the HIV infection and the care of persons with AIDS and their families. Did the NCNR work with OSHA on the development of its blood-borne pathogen standard and efforts to reduce the risk of exposure to HIV by nurses?

Dr. Hinshaw. The NCNR joined other agencies within the Public Health Service in providing comments on early drafts of the OSHA standard on the protection of health care workers from blood borne diseases. We are also supporting a study that addresses safe environments, nursing resources and the quality of patient care in dedicated and non dedicated AIDS units in hospitals.

Mr. Dwyer. How many nurses are estimated to become infected with HIV, hepatitis B, and other blood-borne pathogens each year?

Dr. Hinshaw. There are no reliable national estimates of numbers of nurses or health care workers who become infected with blood borne pathogens. CDC estimates that 12,000 health care workers whose jobs entail exposure to blood become infected with hepatitis B (HBV) each year. For this reason, health care workers are urged to utilize a safe and effective vaccine that has been available since 1982. The CDC surveillance program for health care workers exposed via needlesticks or mucous membrane splashes to HIV infected blood had 1,201 persons enrolled by July 31, 1988. Of these, four were found to be seropositive, a rate of 0.47%.

PEDIATRIC AIDS

Mr. Dwyer. The NCNR budget justification's description of the AIDS Research Program curiously neglects to mention efforts undertaken to treat Pediatric AIDS patients. In New Jersey, Pediatric AIDS is an enormous problem. Five New Jersey metropolitan areas are among the country's top 25 metropolitan areas for Pediatric AIDS infection. In addition, New Jersey also has a high incidence of "border babies", a related problem. What efforts are being made to give labor-delivery and neonatal nurses support and additional training for the care of Pediatric AIDS patients?

Dr. Hinshaw. The NCNR is supporting a study of perinatal transmission of HIV to infants of high risk mothers in a metropolitan area with a high incidence of HIV. Mothers and babies are followed for 36 months to see which infants remain positive, comparing them to infants who remain HIV negative or seroconvert from positive to negative. In addition to biological indices, information is being gathered on growth characteristics, developmental milestones, and sources of infant infections. Maternal HIV antibody serostatus, progression of the disease, and family dynamics are also being documented. Results may support broadening the HIV screening policy during pregnancy and the neonatal period. Early detection of biological markers associated with HIV antibody seropositivity beyond the age of 15 months may

allow targeting of infants eligible for intense medical and nursing follow-up treatment. NCNR has collaborated with other Public Health Service agencies in the planning of training programs, but we do not fund clinical training programs as such. Training programs for the care of pediatric AIDS patients are funded through HRSA.

Mr. Dwyer. What efforts are underway to train visiting nurses and other home care nursing professionals about the special need of Pediatric AIDS patients?

Dr. Hinshaw. The NCNR is supporting several studies that focus on the health and social support needs of AIDS patients and their families at different stages of illness in the home and in other health care settings. Training programs for home care and the special needs of pediatric AIDS patients are provided through HRSA.

Mr. Dwyer. It is my understanding that nurses play an important role in educating foster parents in New Jersey on the special needs of HIV-infected foster children. What will NCNR be doing to improve and support these ongoing programs?

Dr. Hinshaw. Nurses are making major contributions in meeting the special care needs of HIV infected foster children. We anticipate that the results of the longitudinal study of infants from birth to 36 months will provide useful information to practitioners about the causes and number of bacterial infections, growth and development, weight gain as well as the seroconversion rate from positive to negative. Early detection of biological markers associated with HIV beyond the age of 15 months may allow targeting of infants who could benefit from intensive treatment. We will be disseminating information to practicing nurses on the latest findings in the care of HIV infected persons in collaboration with other Public Health Service agencies.

HOSPICES

Mr. Dwyer. With the increase in the numbers of HIV cases and deaths due to cancer and other terminal diseases, the need for nurses trained in the care for the dying becomes more acute. What research efforts has the NCNR undertaken to improve the training of nurses who work in our nation's hospices?

Dr. Hinshaw. As you know, those with AIDS and cancer are now living longer as a result of new scientific discoveries that can prolong their lives and mediate their symptoms and concurrent infections. This delay in the terminal stages of these diseases has opened avenues for research inquiries into the appropriate nursing management of patient symptoms that occur as part of their disease process or secondarily to needed treatment.

NCNR is funding several studies of nursing interventions designed to facilitate the self care of those with cancer and AIDS, and to improve home care provided to these populations. Several NCNR studies are focused on examining the impact of

providing long-term care at home, bereavement as a result of loss of a loved one, and stress on spouses and family caregivers. These studies, when completed, should provide a foundation for targeted intervention studies to assess the most effective means to provide care for these patients, their spouses and other family caregivers. I must clarify that NCNR does not provide support for educational programs, nor do we directly fund institutions to educate nurses to work in hospices or other health care settings.

BIOETHICS AND CLINICAL PRACTICE RESEARCH PROGRAM

Mr. Dwyer. Does the Center's Bioethics and Clinical Practice Research Program provide support for programs which instruct nurses to care for the dying?

Dr. Hinshaw. The Bioethics and Clinical Practice Research Program developed by NCNR staff is designed to stimulate research that examines ethical issues and dilemmas occurring during clinical decision making. This is a small grants and research training initiative that should facilitate investigators' efforts to develop a research program in this area, and provide seasoned investigators the opportunity to begin pilot projects that can lead to larger studies in the future. NCNR does not provide support through the extramural research program for the instruction of nurses to care for the dying, because that effort is outside of our mission, and is part of the mission of the Division of Nursing, HRSA.

HOSPICES

Mr. Dwyer. Are there any specialized programs for treating AIDS patients in hospice?

Dr. Hinshaw. NCNR is supporting one study of home hospice care for persons dying of AIDS with parents as caregivers. Other research efforts focus on nurse managed care of persons with AIDS in their homes in comparison to routine home care. Little research is available to document the effectiveness of this delivery strategy for HIV patients, particularly as it relates to evaluation measures of patient functioning, utilization of services, costs of services, and satisfaction with care. Although I am not aware of a national specialized program for treating AIDS patients in hospice, I know that many hospice programs are caring for AIDS patients.

PRESSURE SORES

Mr. Dwyer. The budget justification states that a more effective treatment for pressure sores will be a priority of the NCNR, because of the suffering that these sores cause. It is my understanding that the Gillis Long Hansen's Disease Center has played an important and unexpected role in the treatment of sores caused by Kaposi's sarcoma in AIDS patients. Has the NCNR been working with the Gillis Long Center to develop a more effective treatment for pressure sores?

Dr. Hinshaw. To the best of my knowledge, the Gillis Long Hansen's Disease Center does not have an extramural research program. NCNR would welcome the opportunity to learn more about promising treatments for the various types of ulcers.

Dr. Dwyer. Will the NCNR be conducting any collaborative research on pressure sores with the National Institute on Aging or the National Institute of Arthritis and Musculoskeletal and Skin Diseases?

Dr. Hinshaw. NCNR is interested in collaborative research on wound healing and pressure sores with the National Institute on Aging, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and the National Institute of General Medical Sciences. Preliminary discussions have been held to explore common interests and promising areas for research.

AWARD RATES

Mr. Pursell. Throughout this subcommittee's hearings for the National Institutes of Health, many members have voiced concerns that we are not spending enough on NIH research. A frequent complaint is that the award rate has decreased in recent years, in spite of the fact that NIH funding continues to increase. What is NCNR's projected award rate for FY 90? For FY 91?

Dr. Hinshaw. The projected award rate for NCNR for FY 1991 is 12 percent, and the estimated award rate for FY 1990 is 19 percent.

Mr. Pursell. How do these figures compare to NIH as a whole?

Dr. Hinshaw. The overall NIH award rate projected for FY 1991 is 25.4 percent, and the NIH award rate estimated for FY 1990 is 24.1 percent.

Mr. Pursell. How do they compare with NCNR award rates for previous years?

Dr. Hinshaw. The last year completed was FY 1989, and in that year, our award rate was 25.1 percent.

RESEARCH MANAGEMENT AND SUPPORT

Mr. Pursell. As a new Institute, NCNR is faced with significant administrative and other start-up costs. What effect has this had on the amount of money you have been able to make available for research?

Dr. Hinshaw. The costs of setting up a new organization are certainly significant, and they are accompanied by many other difficulties. However, the NCNR has been able to fit into the structure of the NIH without an undue level of expense for its establishment.

There are also significant costs involved in administering the programs over time, especially since we are overseeing a vigorous growth in the field of nursing science. We have made every effort to maximize the proportion of our budget that is awarded for extramural research across the country.

PROFESSIONAL JUDGMENT TO 1994

Mr. Pursell. What level of funding do you need to be at say, 3 years from now, i.e., what do you need to be brought up-to-par with the more established institutes?

Dr. Hinshaw. In order to facilitate the rapid momentum of the nursing research community and handle the backlog of research questions which need to be addressed to improve nursing practice, in my judgment approximately $132 million would be a reasonable funding level for FY 1994. This level could be attained over a 3

year period, with a recommended level of $76 million in FY 1992, and $102 million in FY 1993. This would enable us to attain a funding level close to that of some of the smaller research institutes at NIH.

This three year estimate is based on:

- Supporting a 35% award rate, not unusual for new centers or initiatives. Due to the strong response from the community to the establishment of NCNR, we would predict over 430 applications by 1994.

- Expanding the Centers program to 5 Specialized and 6 Exploratory Centers in FY 1992 with another expansion in FY 1994 as recommended by the National Advisory Council on Nursing Research.

- Continuing the strong research training program with an increase in postdoctoral opportunities, initiation of the nurse scientist program, and an increase in research training for minority colleagues.

- Expanding the collaborative intramural research program to nursing research protocols dedicated to nursing care of patients and families facing cancer, and the special care requirements of the elderly.

This is the level of support necessary to put nursing research and research training programs on a par with the research endeavors of the other NIH components. The response from the nursing research community is generating many more exceptional proposals than we originally anticipated. These recommendations for funding will help the NCNR to adequately address its goals of providing nation-wide programs of basic and clinical research in patient care, training of nurse scientists, and the dissemination of research results, while ensuring that the funds will be used responsibly to support only research of outstanding merit.

PROFESSIONAL JUDGMENT BUDGET

Mr. Pursell. What level of funding would you request for FY 91?

Dr. Hinshaw. In my professional judgment, now that the Center has in place solid foundations for substantial extramural and intramural programs, and the community has responded vigorously with numerous proposals for valuable research, the time is right for a major move forward. I will prioritize my opinions on the most vital needs of the Center by funding mechanisms:

1. $7,890,000 would allow restoration of noncompeting and competing research project grants to a 7 percent reduction level, and would increase the number of competing awards to 57, equivalent to a 20 percent award rate.

2. $2,473,000 would permit the second step in development of the research centers program, by adding 3 specialized centers and 4 exploratory centers.

3. $631,000 would allow attainment of the third step of the training initiative, adding 17 trainees to the NRSA program and 6 research career awards, for a total of 280 trainees in 1991. This would include the initiation of the planned Nurse Scientist Award.

4. $433,000 added to the Collaborative Intramural Research Program would permit initiation of the next clinical protocol for nursing care research with HIV-positive patients in the NIH Clinical Center.

5. $3,255,000 in research project grants would bring the number of competing awards to 71, thereby attaining a 25 percent award rate. All of the awards would be reduced 7 percent.

6. $576,000 in Research Management and Support would allow staffing changes without loss of other services or delay of the national planning process to develop a National Nursing Research Agenda.

These needs could all be satisfied with a 1991 budget of $50,385,000 for the NCNR.

AWARD RATES

Mr. Pursell. How much money would you require to get NCNR's award rate equivalent to that of the NIH as a whole?

Dr. Hinshaw. It would take an additional $10.3 million over the President's request for NCNR to achieve a 25 percent award rate in FY 1991.

COST ELEMENTS OF RESEARCH PROJECT GRANTS

Mr. Pursell. It has been said the NCNR-based research is labor-intensive, primarily because it is clinically-based. Does this increase your costs and does it affect your award rate?

Dr. Hinshaw. We have recently studied the cost components of our grants, to see which types of cost are greatest, to compare our grants to NIH as a whole, and to make conclusions about the labor-intensive nature of our research.

The data show that our grants do indeed have a very high proportion of personnel costs, relative to the rest of NIH. In 1989, the NCNR research project grant had over 74 percent of the direct costs devoted to research personnel costs, while over all of the NIH the proportion was somewhat above 67 percent. Further examination of the data showed that the smallest part of our research projects, relative to the rest of NIH, is the supplies category. This category constituted only 2 percent of the direct costs of NCNR grants, while it represented 14 percent NIH-wide.

I believe that this is the largest factor in the growth of the average size of NCNR's research project grants. Although our grants have grown vigorously in the few years of the Center's existence, our average cost is still less than the NIH-wide average.

LOW BIRTHWEIGHT INFANTS

Mr. Pursell. One of NCNR's research priority areas is the prevention and care of low birthweight babies, and the related effort to reduce infant mortality. Please identify for the Subcommittee several examples of NCNR research in this area.

Dr. Hinshaw. One example of a study related to the prevention of low birthweight infants through the prevention of premature labor is a study of home management of pre-term labor. The second example is an interdisciplinary, intervention study with high risk minority families. In the second study, the scientists will examine nursing interventions of frequent contacts and support to reduce the incidence of premature labor. One investigator is examining the responses and outcomes of pregnant, homeless women, and another is examining factors affecting a woman's use of health behaviors that support more positive outcomes in the pregnancy and infant.

NCNR research related to low birthweight infants and infant mortality include a study of infant growth failure, studies of maternal-infant interaction with high risk infants, and a comparison of mothers of infants with handicaps and mothers with full term infants, and a longitudinal study of infants at risk for AIDS.

NCNR is also involved in several studies related to the care of the low birthweight infant, including studies of infant responses to care activities such as handling, feeding, and other procedures. Also included are studies of the low birthweight infant's ability to demonstrate their readiness for feeding and to determine the energy expenditure for feeding.

We are learning the significance of care procedures on the low birthweight infant and that the infant's responses to care procedures are influenced by the behavior and organizational state of the infant. Clinical trials to test further the care procedures and the responses of the infant are necessary to reduce infant morbidity. We know from nursing research that low birthweight infants may have ongoing problems including some behavioral and learning problems not apparent until the child enters school. We need to continue to study these children over time and to study the care they receive in the neonatal units and the interventions through early childhood.

Mr. Pursell. I am presently working with local officials in Jackson, Michigan to help improve access to prenatal care for low-income women. As we know, one of the major factors responsible for high infant mortality and low birthweight is lack of access to prenatal care. Have any studies been conducted to determine whether high-risk pregnant women, particularly teenagers, follow

the recommendations of their physician, when they have access to a physician?

Dr. Hinshaw. A concern related to access to care for the pregnant teenagers is that they tend to delay seeking prenatal care. It is also known that many factors influence whether a person responds to the recommendations of a health professional. NCNR is funding multifactorial research testing interventions that include home visits and phone calls, to increase the support to the high risk pregnant woman or teenager. In another study of why women seek or do not seek early prenatal care the investigator is also studying the patterns of health care use by these mothers and their infants for 1 year following birth.

Mr. Pursell. Is NCNR involved in any studies regarding post-partum care and its affect on infant mortality and infant and child nutrition, illnesses, injuries, and abuse?

Dr. Hinshaw. NCNR is funding research to examine the care of infants with birth defects to determine altered care patterns and determine interventions to support the mother and infant. A study conducted in two sites in Michigan examines the developmental progress of the low birthweight and full term infant in relation to parental responses and family functioning from birth through 18 months.

Another study being cofunded by NCNR is examining pre and postnatal nurse home visitation services for socially disadvantaged women. The nurse intervention is directed to improve the women's prenatal health habits, infant caregiving skills, mental health functioning, use of community services, educational and occupational achievements, and to reduce unplanned additional pregnancies. The children are evaluated on the incidence of low birthweight, growth and nutrition, accidents, and abuse and neglect. Previous work by this investigator suggests that if nurse home-visitation services are properly targeted, designed, and conducted, they can have a significant effect on the well being of children and parents at risk.

AIDS RESEARCH

Mr. Pursell. As the number of AIDS patients increases and hospitals and other health care facilities are faced with more patients and higher costs, costs often not covered by insurance, more emphasis will be placed on lower cost alternatives, including at-home and hospice care. Please describe the types of AIDS research being conducted by NCNR.

Dr. Hinshaw. One of the studies we are supporting addresses the nursing care needs of patients across five different care settings. We expect that the results of this study will be useful in developing a classification system for nursing care of AIDS patients, and may also contribute to nursing education programs based on new knowledge about stage-specific patient needs. This may also clarify some situations in which at-home care is appropriate instead of hospital care, lowering the care cost and improving the quality of life for AIDS patients.

Another one of our projects which may address the concerns you have raised is a study of the quality of nursing care of people with AIDS who have Pneumocystis carinii pneumonia (PCP). These patients will be followed from their first hospitalization with PCP infection for a period of 6 months. The relationship between specific nursing interventions and short- and long-term patient outcomes will be studied. The results of this study may help us to define the most effective and most efficient use of hospital resources for treatment of this infection.

CAREGIVING AND ALZHEIMER'S DISEASE

Mr. Pursell. The percentage of our nation's population over age 65 is growing rapidly. These people, particularly those over age 75, are faced with special needs and health care problems. What activities is NCNR conducting in the area of care for the elderly? Does this include any special projects relating to care for Alzheimer's patients?

Dr. Hinshaw. The NCNR has great interest in research that impacts on the health care problems of the growing number of elderly persons in our nation. Many of our projects that are focused on managing and preventing chronic disease seek knowledge that will mitigate the effects of these diseases in the elderly.

An area of special interest to us during the past year is that of investigating frailty and prevention of injuries in elderly persons. We have been working jointly with the National Institute on Aging in this area. In FY 1989, we published a request for applications inviting cooperative agreement proposals focused on the frail elderly. Forty four applications were received in response to this invitation, and after review of these applications, eight research projects and one coordinating center will be cofunded by the NCNR and the NIA. This initiative will begin on April 15, 1990 and findings from these sites across the country will provide needed data to identify the many factors that contribute to frailty in the elderly, and to test strategies that will prevent injuries due to frailty.

Care for patients with Alzheimer's Disease is also a major interest of the NCNR. Both families and professional caregivers continue to seek effective strategies for managing this disease and its devastating consequences to the patient and the family. In FY 1989, 11 research project applications totaling $2.5 million were received. We are currently funding $1,437,000 in this area.

In an effort to stimulate further research projects and applications for research training, in FY 1989, the NCNR published a program announcement jointly with the National Institute on Aging which focused on issues in caregiving in Alzheimer's Disease. We also issued a program announcement encouraging applications for research training in the area of Alzheimer's Disease and encouraging applicants to seek training at established centers for research on Alzheimer's disease.

RURAL HEALTH RESEARCH

Mr. Pursell. Congress encouraged NCNR to expand its research efforts in rural health care and provided an additional $600,000 for this program in FY 90. Please explain your activities in this area.

Dr. Hinshaw. Rural health care is an area of particular interest to NCNR. My staff have been active in evaluating the needs of those residing in rural areas, and have determined that the health of minority populations could be improved through the development and evaluation of community-based nursing practice models. These models will be targeted on the most vulnerable of minority persons, namely those over 65 years of age, childbearing women, adolescents at risk for early pregnancy, children and infants. In March, we published, in cooperation with the Division of Nursing, HRSA and the new Agency for Health Care Policy and Research, a request for applications for research and demonstration project applications to be submitted on June 15, 1990. A total of $1,500,000 is available from all three agencies, including the $600,000 provided to NCNR. The combined level of support will enable us to fund two or three proposals during FY 1990.

RESEARCH TRAINING

Mr. Pursell. The nursing research community has expressed the need for a strong initiative in research training for nurses. What are you doing in this regard?

Dr. Hinshaw. In 1987, the NCNR defined a multi-year initiative in research training, with the ultimate goal of reaching an annual level of 320 nursing research trainees supported, as recommended by the National Academy of Sciences.

From a base of 171 trainees in 1987, the first step of the initiative was completed in FY 1988, with 194 trainees supported through the National Research Service Award fellowships and institutional training grants, as well as Academic Investigator Awards and Clinical Investigator Awards under the research career awards program. The second step of the initiative was completed in 1989, with 228 trainees supported. The third goal of 270 for 1990 has been adjusted to 257.

The Center has also emphasized the need for additional minority nurse scientist trainees through several special efforts. All of the institutional training grant institutions have been contacted about the availability of supplements for adding minority nurse trainees to their programs. Two of the institutions succeeded in carrying this out in FY 1989, and we are expecting further success. The new research centers are also required to include a minority outreach component, which may involve training of minority investigators.

Mr. Pursell. What are you doing in the area of postdoctoral training?

Dr. Hinshaw. Increased support of postdoctoral trainees has been a key part of NCNR's multi-year training initiative. In FY 1989, 41 postdoctoral trainees were supported, representing 18 percent of the 228 total trainees that were supported that year. Nine of the trainees were on Academic Investigator Awards or Clinical Investigator Awards, 13 were postdoctoral fellows or senior fellows, and the remaining 19 were in postdoctoral training positions under institutional training awards.

As a continuation of the emphasis on increased postdoctoral training support, we estimate we will support 52 post-docs in FY 1990, and the same number will be supported in FY 1991.

We also hope to begin a Nurse Scientist Program as another means of increasing the postdoctoral proportion of our trainees. This will be similar to the Physician Scientist and Dental Scientist Programs of many of the other institutes. This will provide a special opportunity to build a cadre of clinical nurse researchers with a background of rigorous scientific training.

HEALTH AND BEHAVIOR RESEARCH

Mr. Pursell. What studies are being conducted by NCNR in health and behavior?

Dr. Hinshaw. In FY 1989, the NCNR supported research and research training totalling $12,558,000 in the area of health and behavior. We realize that the greatest potential for impacting on health and preventing disease in this century is through behavior changes, and nurses are in the forefront of assessing these behaviors, enabling patients to learn them, and reinforcing their continued performance.

Examples of studies in this area include those focused on behaviors to lower risk and prevent disease, and those that minimize the effects of illness. A longitudinal study of school-age twins is examining physiological, behavioral, and lifestyle factors that contribute to risk for cardiovascular disease. Identification of children at risk for heart disease due to these factors will allow for effective teaching by school nurses and families, and children will be able to form habits that will enhance their health based on scientific conclusions.

Practices of breast self examination for early detection of cancer in women are being studied, as well as the effectiveness of strategies to minimize the debilitating effects of chemotherapy or radiotherapy in cancer treatment. Prevention and early detection of cancer can lower the risk of death from this disease, and function can be improved if symptoms from treatment can be managed.

RESEARCH CENTERS

Mr. Pursell. What is the status of the new Centers program initiated by Congress in 1989? How many applications were received and funded?

Dr. Hinshaw. The new program of centers of excellence in nursing research was indeed begun in 1989. We received a vigorous and enthusiastic response when we published the announcements for the specialized centers and the exploratory centers. There were 11 applications received for the specialized centers, of which we funded two, and 32 applications were received for the exploratory centers, of which we awarded two.

The Specialized Centers are located at the University of Pennsylvania, with a research emphasis on Advancing Care in Serious Illness, and at the University of Washington, with a research emphasis on Women's Health Research. The Exploratory Centers are at the University of Minnesota, with an emphasis on Long-Term Care of the Elderly, and at the University of Pittsburgh, with an emphasis on Critical Care Nursing.

NATIONAL NURSING RESEARCH AGENDA

Mr. Pursell. Please describe the research priorities in NCNR's long-term planning agenda, the National Nursing Research Agenda. Which of these priorities have been started?

Dr. Hinshaw. Seven broad priorities were initially identified by the Steering Committee to the National Nursing Research Agenda (NNRA). They are: HIV Infection: Prevention and Care; Low Birthweight: Mothers and Infants; Long-term Care for Older Adults; Symptom Management; Information Systems for Improving Nursing Care; Health Promotion in Children and Adolescents; and Technology Dependency Across the Lifespan. These have been widely publicized and discussed by NCNR staff, and have already had the effect of stimulating research in some of these areas, even though the refinement of the priorities by expert panels has not yet been completed. Expert panels for the last two priority areas will be constituted in FY 1991.

The first program announcement based specifically on the work of one of the expert panels was published in December 1989. It addressed the physical care of the low birthweight infant, one of the highest priorities of the low birthweight panel. Because low birthweight infants are very fragile and highly subject to complications compared to full-term newborns, especially sensitive nursing care is required. However, the expert panel found very little research that would give direction to the nursing care of these infants. The program announcement, therefore, solicits applications which propose research addressing issues of feeding, respiratory care, skin care, and physical positioning of low birthweight infants. We expect that the research to be funded by NCNR as a response to this program announcement will significantly enlarge the knowledge base on which nursing care of these infants can be based and enhance the quality of the care provided.

In the field of AIDS care, achieving successful prevention and delivering optimum acute and long-term nursing care to persons with AIDS and their families are priorities for the NCNR. NCNR is working with other PHS agencies to encourage studies that test the most effective interventions to ameliorate physiological and psychological symptoms. We have also joined other agencies in encouraging research that targets at-risk populations to test prevention strategies.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Center for Nursing Research

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NATIONAL INSTITUTES OF HEALTH

National Center for Nursing Research

For carrying out section 301 and title IV of the Public Health Service Act with respect to nursing research, [33,969,000] $35,127,000

(Departments of Labor, Health and Human Services, and Education, and Related Agencies Act, 1990.)

NATIONAL INSTITUTES OF HEALTH

National Center for Nursing Research

Amounts Available for Obligation 1/

	1989 Actual	1990 Appropriation	1991 Estimate
Appropriation	$29,500,000	$33,969,000	$35,127,000
Sequester order	---	-422,000	---
Enacted administrative reductions	-361,000	-34,000	---
Subtotal, adjusted appropriation	29,139,000	33,513,000	35,127,000
Real transfer to the Health Resources and Services Administration for AZT grants	6,000	---	---
Comparative transfer to: DRR for administration of RCMI Program	-1,000		
Comparative Transfer from: OD/NIH for FTE increase	63,000		
Subtotal, adjusted budget authority	29,195,000	33,513,000	35,127,000
Unobligated balance lapsing	-15,000	---	---
Total obligations	29,180,000	33,513,000	35,127,000

1/ Excludes the following amounts for reimbursable activities carried out under this account: 1989 -- $2,133,000; 1990--$2,817,000; 1991--$3,200,000.

NATIONAL INSTITUTES OF HEALTH

National Center for Nursing Research

Budget Mechanism
(Dollars in thousands)

	1989 Actual		1990 Appropriation		1991 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Grants:						
Research projects						
Noncompeting	80	$12,641	94	$14,803	106	$17,785
Admin. supplemental	(8)	297	(6)	302	(6)	302
Competing						
Renewal	10	2,025	9	2,163	6	1,475
New	39	5,813	35	6,205	26	5,144
Supplemental	1	64	1	112	1	125
Subtotal, competing	50	7,902	45	8,480	33	6,744
Subtotal, res. proj.	130	20,840	139	23,585	139	24,831
Research Centers	4	1,464	4	1,235	4	1,235
Other Research						
Research career program	9	571	12	904	12	904
Other res. related	4	259	4	217	4	217
Subtotal, other res.	13	830	16	1,121	16	1,121
Total, research grants	147	23,134	159	25,941	159	27,187

Training:						
Individual awards:						
Noncompeting	81	1,020	116	1,551	96	1,254
Competing						
New	69	987	35	483	55	780
Subtotal, individual	150	2,007	151	2,034	151	2,034
Institutional awards						
Noncompeting	63	1,329	59	1,276	76	1,711
Competing						
New	6	111	35	910	18	488
Subtotal, Institutional	69	1,440	94	2,186	94	2,199
Total, training	219	3,447	245	4,220	245	4,233
Research and development contracts	1	100	3	351	4	359
Intramural research	FTE		FTE		FTE	
	--	---		202	2	266
Research management and support	30	2,514	30	2,799	35	3,082
	30	29,195	30	33,513	37	35,127
HIV/AIDS	(2)	(761)	(2)	(987)	(4)	(1,148)

NATIONAL INSTITUTES OF HEALTH

National Center for Nursing Research

CROSSWALK - 1989 Actual
(Dollars in thousands)

PROGRAM ACTIVITY	MECHANISM: Research Grants: Research Projects	Research Grants: Research Centers	Research Grants: Other Research	Training Programs: Individual	Training Programs: Institutional	Research & Development Contracts	Intramural Research	Research Management & Support	Total
Nursing Research	$20,840	$1,464	$830	$2,007	$1,440	$100	---	---	$26,681
Intramural Research	---	---	---	---	---	---	---	---	---
Research management and support	---	---	---	---	---	---	---	$2,514	2,514
Total	20,840	1,464	830	2,007	1,440	100	---	2,514	29,195

NATIONAL INSTITUTES OF HEALTH

National Center for Nursing Research

CROSSWALK - 1990 Appropriation
(Dollars in thousands)

	MECHANISM								
	Research Grants			Training Programs		Research & Development		Research Management	
PROGRAM ACTIVITY	Research Projects	Research Centers	Other Research	Individual	Institutional	Contracts	Intramural Research	& Support	Total
Nursing research	$23,585	$1,235	$1,121	$2,034	$2,186	$351	---	---	$30,512
Intramural research	---	---	---	---	---	---	$202	---	202
Research management and support	---	---	---	---	---	---	---	$2,799	2,799
Total	23,585	1,235	1,121	2,034	2,186	351	202	2,799	33,513

NATIONAL INSTITUTES OF HEALTH
National Center for Nursing Research

CROSSWALK - 1991 Estimate
(Dollars in thousands)

PROGRAM ACTIVITY	MECHANISM								
	Research Grants			Training Programs		Research & Development	Intramural	Research Management	
	Research Projects	Research Centers	Other Research	Individual	Institutional	Contracts	Research	& Support	Total
Nursing Research	$24,831	$1,235	$1,121	$2,034	$2,199	$359	---	---	$31,779
Intramural Research	---	---	---	---	---	---	$266	---	266
Research management and support	---	---	---	---	---	---	---	$3,082	3,082
Total	24,831	2,235	1,121	2,034	2,199	359	266	3,082	35,127

NATIONAL INSTITUTES OF HEALTH

National Center for Nursing Research

Summary of Changes

1990 Estimated budget authority	$33,513,000
1991 Estimated budget authority	35,127,000
Net change	+1,614,000

Changes:	1990 Current Estimate Base Pos. (FTEs)	Amount	Change from base Pos. (FTEs)	Budget Authority
A. Built-in:				
1. Within-grade increases		$1,874,000		+$21,000
2. Annualization of 1990 payraise		1,874,000		+16,000
3. One extra day of pay		1,874,000		+7,000
4. Cost of January 1991 payraise		1,874,000		+80,000
5. Federal Employees Compensation Fund		7,000		+0
6. Unemployment compensation increase		3,000		+0
7. FTS rate increase		21,000		+1,000
8. Payment for centrally furnished services		407,000		+197,000
9. Service and supply fund increase		125,000		+2,000
10. Increased cost of laboratory materials and other supplies		735,000		+24,000
11. DHHS Working Capital Fund		28,000		-1,000
Subtotal				+347,000
B. Program:	No.	Amount	No.	Amount
1. Research projects grants:				
a. Noncompeting	94	15,105,000	+12	+2,982,000
b. Competing	45	8,480,000	12	-1,736,000
Total	139	23,585,000	+0	+1,246,000
2. Research training		4,220,000		+13,000
3. Research and development contracts		351,000		+8,000
Subtotal		78,156,000		+1,267,000
Total changes				+1,614,000

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National Center for Nursing Research

Budget Authority by Activity

	1989 Actual		1990 Appropriation		1991 Estimate	
	FTE	Amount	FTE	Amount	FTE	Amount
Nursing research		$26,681,000		$30,512,000		$31,779,000
Intramural research	---	---	---	202,000	2	266,000
Research management and support	30	2,499,000	30	2,799,000	35	3,082,000
Subtotal, obligations		29,180,000		33,513,000		35,127,000
Unobligated balance lapsing		15,000		---		---
Total budget authority	30	29,195,000	30	33,513,000	37	35,127,000
HIV/AIDS	(2)	(702,000)	(2)	(987,000)	(4)	(1,148,000)

NATIONAL INSTITUTES OF HEALTH

National Center for Nursing Research

Budget Authority by Object

	1990 Appropriation	1991 Estimate	Increase or Decrease
Total number of full-time permanent positions	34	38	+4
Total compensable workyears: full-time employment	30	37	+7
full-time equivalent of overtime and holiday hours	1	1	---
Average ES salary	$76,922	$92,302	+$15,380
Average GM/GS grade	12.4	12.4	---
Average GM/GS salary	36,646	37,635	+989
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	58,486	60,065	+1,579
Average salary of ungraded positions	---	---	---
Personnel compensation:			
Full-time permanent	1,695,000	2,177,000	+482,000
Other than full-time permanent	136,000	169,000	+33,000
Other personnel compensation	63,000	77,000	+14,000
Subtotal, personnel compensation	1,894,000	2,423,000	+529,000
Personnel benefits	333,000	412,000	+79,000
Travel and transportation of persons	50,000	58,000	+8,000
Transportation of things	5,000	6,000	+1,000

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Budget Authority by Object

	1990 Appropriation	1991 Estimate	Increase or Decrease
Rent, communications and utilities	40,000	42,000	+2,000
Printing and reproduction	40,000	41,000	+1,000
Other services:			
Project contracts	351,000	79,000	-272,000
Centrally furnished services	407,000	604,000	+197,000
Other	151,000	---	-151,000
Supplies and materials	11,000	12,000	+1,000
Equipment	70,000	30,000	-40,000
Grants, subsidies and contributions	30,161,000	31,420,000	+1,259,000
Total, budget authority by object	33,313,000	35,127,000	+1,614,000

NATIONAL INSTITUTES OF HEALTH

National Center for Nursing Research

Significant Items in House Appropriations Committee Report

Item	Action Taken or to be Taken
1990 House Report	
Commission on Nursing	
1. The Committee intends that the Secretary allocate $275,000 to be transferred from this account, to maintain the Commission on Nursing for a period of one year, ending on September 30, 1990. (page 84)	1. An agreement has been executed with the Bureau of Health Professions, Health Resources and Services Administration to transfer $272,000 to pay the expenses of the Commission. This amount reflects the required sequestration.

NATIONAL INSTITUTES OF HEALTH

National Center for Nursing Research

Significant Items in Senate Appropriations Committee Report

Item	Action Taken or to be Taken
1990 Senate Report	
Rural Health Care	
1. The National Center for Nursing Research has the opportunity to focus additional nursing research on subjects and issues that will assist rural nurses in performing their duties. The committee has added $600,000 for this purpose, which will permit the National Center for Nursing Research to double its rural nursing research portfolio. (page 39) The Committee continues to urge that serious attention be given to the health needs of rural Americans. (page 157)	1. Research on rural health care will receive emphasis in 1990, with the goal of supporting $1,600,000 in projects addressing the health needs of rural populations and the problems facing nurses providing care in rural areas.
2. The Committee urges that the nursing shortage continue to be analyzed through a variety of research efforts. (page 156)	2. The Center continues to increase its support for research and research training focused on strategies to increase nursing resources and improve the quality of care. Research on two innovative nursing care delivery models is being supported cooperatively with the Division of Nursing in the Health Resources and Services Administration.

NATIONAL INSTITUTES OF HEALTH

National Center for Nursing Research

Significant Items in Appropriations Conference Report

Item	Action Taken or to be Taken
1990 Conference Report	
1. The conferees also encourage the Secretary to appoint a nurse as an Assistant to the Secretary to assist in the implementation of the Commission's recommendations, and to serve as an advisor to the Secretary on health care policy matters which affect nursing. (page 22)	1. The 1990 proposed Commission on Nursing, consisting of nurses and non-nurses, will be available to the Secretary in an advisory capacity on health care policy matters which affect nursing.

NATIONAL INSTITUTES OF HEALTH

National Center for Nursing Research

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1990 Amt. Authorized	1990 Appropriation	1991 Amt. Authorized	1991 Budget Estimate
Research and Investigation	Section 301	42§281	Indefinite	$29,749,000	Indefinite	$30,894,000
National Center for Nursing Research	Section 483 and 484	42§287	Indefinite		Indefinite	
National Research Service Awards	Section 487	42§288	Such sums as Necessary 1/	4,220,000	Authorizing Legislation to be Requested	4,233,000
Total Budget Authority				33,969,000		35,127,000

1/ This training authority is shared with other research training programs of the National Institutes of Health and the Alcohol, Drug Abuse, and Mental Health Administration.

NATIONAL INSTITUTES OF HEALTH

National Center for Nursing Research

Appropriations History 1/

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1987	---	$16,700,000	$20,000,000	$20,000,000
1988	$16,133,000	24,744,000 2/	23,566,000	23,380,000
1989	24,400,000 3/	27,417,000 4/	28,107,000	29,139,000
1990	29,970,000 5/	32,969,000	34,969,000	33,969,000
1990 Sequester				-422,000
1991	35,127,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Does not include funding for AIDS research consolidated at the Secretary's level.

3/ The 1989 request excludes funds for AIDS research and education ($707,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

4/ Research training is excluded, due to lack of authorization.

5/ The 1990 request excludes funds for the National HIV Program ($999,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

Justification

National Center for Nursing Research

	1990 Appropriation		1991 Estimate		Increase or Decrease	
	FTEs	BA	FTEs	BA	FTEs	BA
TOTAL	30	$33,513,000	37	$35,127,000	+7	+$1,614,000
HIV/AIDS	(2)	(987,000)	(4)	(1,148,000)	(+2)	(+161,000)

General Statement

The National Center for Nursing Research (NCNR) supports a nation-wide program of basic and clinical research in patient care, training of nurse scientists, and dissemination of research results. As the base of nursing science expands, health care can become more effective and efficient, and the quality of life for millions of Americans who receive care each year can be enhanced.

Nursing research includes scientific inquiry into fundamental biological, biomedical, and behavioral processes that underlie health and the environment in which health care, especially patient care, is delivered. In the pursuit of new knowledge, nursing research involves studies of effective health care in homes, hospitals, nursing homes, communities, and peoples' places of work. These investigations examine human biology and behavior in both health and illness, including the processes that lead to changes in health and the behaviors associated with critical life events. The focus may be on health promotion, environmental influences on health, or the care of acutely or chronically ill persons. Another major aspect of nursing research is the study of therapeutic actions that lessen the effects of illness and increase the ability of individuals and their families to cope with health problems.

The programs of the Center have advanced considerably in the past year, with award of the first research center grants, completion of the second step of the research training initiative, publication of the reports of the first two priority expert panels for the National Nursing Research Agenda -- low birthweight infants and HIV infection research, development of research initiatives for those two areas, and the establishment of a new program of research in bioethics and clinical practice. These programs will be continued in 1991, with an increased emphasis on basic research.

Overall Budget Policy

The FY 1991 budget request for the National Center for Nursing Research favors basic research and totals $35,127,000, an increase of $1,614,000 above the 1990 level. A total of $24,831,000 will be devoted to research project grants, with each award reduced about 17 percent from the committed or

approved amount. The request will support 33 competing project grants at an average cost of $204,364, and 106 noncompeting research project grants at an average cost of $167,783. In 1990, 94 noncompeting and 45 competing research project grants are being supported.

The NCNR initiated its Research Centers program in FY 1989 by establishing two Specialized Centers and two Exploratory Centers for Nursing Research. The total support in FY 1991 will be $1,235,000.

The FY 1991 request will provide $904,000 for 12 research career awards, the same number as in 1990. Four other research related awards, will be supported for $217,000.

The Center's research training program will support a total of 245 trainees through individual research fellowships and institutional training grants. The total to be awarded in research training is $4,233,000 in 1991, an increase of $13,000 over the 1990 level.

Research and development contracts will be funded at a level of $359,000 in 1991, an increase of $8,000 over the 1990 level.

The intramural research program was newly established in 1990. It will be supported at a level of $266,000 in 1991, which is an increase of $64,000 over 1990, and includes the cost of the January, 1991 payraise.

Research management and support activities will be conducted at a level of $3,082,000 in 1991, an increase of $283,000 over 1990. Seven additional FTEs in 1991 represent staff needed to manage the increasing range of programs, handle the rapidly growing number of applications, perform planning and evaluation activities, and carry out necessary administrative functions not previously possible, including data processing and information systems support. The salary cost of these FTEs will be provided for through reductions of equipment purchases, travel, and other services.

Program Accomplishments

The National Center for Nursing Research has initiated a new Collaborative Intramural Research program, to allow nursing science to participate in the enormous research opportunities on the Bethesda campus of the NIH. The first protocols are being established in symptom management and the care of HIV-positive patients, and future years will witness the expansion of this program into other areas of patient care.

The first two Priority Expert Panels within the planning effort to define a National Nursing Research Agenda have completed their work and reported to the nursing research community. Specific areas of greatest need and promise for scientific advances were outlined and prioritized in the research fields of the care of HIV-positive persons and the prevention of and care for low birthweight infants.

The Center initiated a new research centers program, with the award of two Exploratory Centers and two Specialized Centers for Nursing Research. These centers are now beginning to address a wide spectrum of health care concerns, from women's health to long term care of the elderly, and promise to offer new tools for patient care in critical care nursing and the behavioral aspects of a number of different diseases.

Efforts to encourage minority nurses to undertake research training and to participate in research projects are growing stronger and more diverse. New requirements for all institutional training grants funded by the Center and minority outreach aspects of the new research centers are recent accomplishments.

The NCNR's research training initiative has succeeded in increasing both the total number of nurses training as investigators and the proportion pursuing postdoctoral research training. The newly initiated program in Bioethics and Clinical Decision Making is initially being pursued through the training and research career award mechanisms, to bring talent into this important field.

Nurse scientists are pursuing a number of different strategies to characterize the family caregiving process and to seek ways of relieving the heavy burden which caring for an elderly relative can become over time. Current research projects are investigating the adequacy of community support programs for both the elderly patients and their caregivers, with special attention given to the needs of rural populations.

As a result of the nursing research community defining the research needed in low birthweight, the Center has initiated a major initiative to advance this research. Current projects are addressing various aspects of prevention of low birthweight, including the role of visiting nurses in improving prenatal health and infant care practices among poor, unwed young mothers, and a social support program for pregnant black women lacking the support of a mother and/or spouse. Research also is adding to our knowledge of the best care methods for low birthweight infants in the neonatal intensive care unit, with some choices producing better weight gain and quicker development, and more informed care by parents upon discharge from the hospital.

NCNR continues to bring research efforts to bear on the substantial clinical problem of pressure sores among bedridden patients. Research into the various factors making different classes of patients likely or unlikely to develop pressure sores should enable care providers to better predict them before they develop. Study of possible new methods of curing sores which are already developed includes such methods as transcutaneous electrical nerve stimulation.

Behavioral research is major avenue toward better health promotion and patient care, and is a major component of the Center's mission. Major studies underway hold promise for establishing the best methods of assisting patients during recovery from major operations including heart transplants and colorectal surgery. Studied of healthy behaviors and risk-taking behaviors among adolescents may prove useful to nurses, educators and parents.

Several of the Center-supported studies encompass differences in health care in rural and urban areas, together with strategies for nurses to pursue in fulfilling their special roles in rural health care. Center staff participate in managing two cooperative agreements to test innovative models of nursing practice in acute care hospitals, including comparison of rural settings, which hold promise for significant improvements in patient care and the best use of nursing resources.

A recent emphasis in rehabilitation research has been the frail elderly. The prevention of falls, assessment of capabilities, and the best methods of returning the patient to full functioning are research subjects of NCNR-supported scientists, which are growing importance in the face of a growing population of older Americans.

The Center is continuing to emphasize research addressing the root causes and possible solutions for the problem of shortages of qualified nurses. Different methodologies for management of nursing staff, job factors and aspects of the nurse-patient relationship are being investigated, in order to improve the use of nursing resources and to bring the most benefits possible to the patient.

AIDS Research Program

NCNR AIDS Program

NCNR is committed to the conduct and support of basic and clinical research which focuses on the physical, psychosocial, and ethical problems central to prevention of HIV infection and the care of persons with AIDS (PWAs), their partners and families. Four research project grants and an institutional training grant totaling $702,000 were awarded in FY 1989. In FY 1990 NCNR has continued its support for AIDS research, training, and information activities, and expects to award $987,000 in research and research training. NCNR will devote increased funding to extramural AIDS research activities in FY 1991, at a requested level of $1,148,000, and plans to increase its intramural program of AIDS research.

Recent Program Accomplishments

The NCNR intramural program for HIV infection research, initiated in 1990, is being conducted in collaboration with the National Institute for Allergy and Infectious Diseases (NIAID) and the NIH Clinical Center, and will be modestly expanded in 1991. NCNR intramural investigators will conduct basic and clinical research in symptom management, seeking to minimize the harmful effects of the infection and treatments, such as unintentional weight loss, diarrhea, fatigue, oral complications, dementia, anxiety, and depression. As long as HIV infection remains incurable, and with advanced treatments allowing individuals to live longer, it is important to discover ways to decrease morbidity and to diminish the economic and personal costs of infection and treatment.

The NCNR is supporting a study of the quality of care provided to PWAs with Pneumocystis carinii pneumonia (PCP), beginning at the time of the first hospitalization and continuing through six months of treatment. Patients with PCP and nurses who deliver their care are being interviewed to ascertain the most common problems, and specific interventions will be evaluated.

Another NCNR-supported research project is assessing the care needs of PWAs in different treatment settings: dedicated outpatient and inpatient AIDS units, home care agencies and nursing homes. Data on morbidity and mortality, as well as information pertinent to patient demographics, access to health care, psychosocial adjustment, and support systems are being obtained and evaluated.

Research Plans

Through the process of defining a National Nursing Research Agenda (NNRA), the Center has identified priorities for nursing research on HIV infection and AIDS. These include identifying target populations for the testing of prevention programs to curtail HIV transmission, testing interventions to ameliorate physiological and psychological symptoms, and determining the optimal mode and mechanism of nursing care delivery.

National Center for Nursing Research

Nursing Research

1991 Authorization: Indefinite

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$30,512,000	$31,779,000	+ $1,267,000

Purpose and Method of Operations

The goals of nursing research are to develop new knowledge that will decrease the vulnerability of people to illness or disability throughout their lives, and to achieve improvement in nursing practice, patient health, and recovery from illness. This extramural activity is comprised of three components:

- Health Promotion and Disease Prevention research -- health promotion addresses the role of nurses in promoting good health practices among the general population, whereas disease prevention research includes measures that are applicable to efforts to intercept the onset of particular illnesses or disabilities.

- Acute and Chronic Illness research -- is concerned with responses to and treatment of illnesses and disabilities throughout the life span. These health care efforts include consideration of biomedical, behavioral, and environmental factors that contribute to the causes, prevalence, amelioration, and remediation of illness and disability.

- Nursing Systems research -- is concerned with quality of care that facilitates patient well-being, the environment in which patient care is delivered, approaches to nursing management, nursing resource utilization, effective patient care delivery, and ethical issues relating to patient care and clinical decisions by patients, families, and health care providers.

The NCNR utilizes a wide variety of research project grant, research career award, research center, and research training mechanisms to advance nursing science and consequently improve patient care in our nation. The following program descriptions are intended to illustrate some of NCNR's high-priority areas of scientific support.

Centers for Nursing Research

The NCNR initiated its Research Centers program in FY 1989 by establishing two Specialized Centers and two Exploratory Centers for Nursing Research. Extensive interest was created in the nursing science field, many applications were received, and competition was intense. Although only four awards were

made, the centers are diverse in their research foci and promise to produce depth in the science of nursing practice.

The Specialized Center for Nursing Research at the University of Washington is establishing a Center for Women's Health Research to emphasize women's health across the lifespan. Research studies address issues such as midlife women's menstrual experiences, the relationship of reproductive hormone status and health perceptions, the effects of ovarian hormones on gut structure and function, biologic and behavioral reactivity in the recovery of middle-aged women who abuse alcohol or benzodiazepines, circadian body temperature rhythms, and the waning of fertility in midlife women.

The Specialized Center for Nursing Research at the University of Pennsylvania is establishing a Center for Advancing Care in Serious Illness. Research projects are focusing on variables influencing functional status of breast cancer patients after diagnosis, the study of depression in stroke patients, the health effects of bereavement, and aspects of the early recovery stages of patients with colorectal cancer.

The Exploratory Center for Nursing Research at the University of Pittsburgh is establishing a Center for Research in Critical Care Nursing which will address a broad range of issues in the prevention and management of critical illness. Studies to be supported include social support and recovery following heart transplantation, comparison of care techniques for ventilated patients, the relationship between injuries in children and their family life events, and family adjustment to critical illness for patients admitted to hospital intensive care units.

The Exploratory Center for Nursing Research at the University of Minnesota is a Center for Nursing Research in Long Term Care of the Elderly. Research is addressing factors which influence the autonomy and independent functioning of older persons with regard to maintenance and promotion of health. Studies include care utilization following treatment for alcohol or substance abuse, clinical nursing interventions to prevent and manage aggressive behavior by cognitively impaired older people in nursing homes, relating performance of activities of daily living with measures of cardiovascular and postural stability to attempt to prevent falls among hospitalized elders, assessment of the needs of older persons upon discharge from the hospital, and study of the optimal mix of formal and informal caregiving services in the home.

Minority Research

The Center is supporting a variety of research projects that examine health problems which disproportionately affect minority populations. These focus on prevention of infant mortality and low birth weight, controlling hypertension in older minority populations, prevention of HIV transmission, care of AIDS patients, and issues in caregiving and the long term care of older people.

The NCNR is participating with other institutes of the NIH in implementing an initiative to provide special research opportunities for minority faculty and students through special supplements to existing awards and through several new dedicated award mechanisms. In the area of training, NCNR has funded slots for minority trainees on existing institutional training grants and for minorities as research assistants on existing research projects. NCNR has

also required the new Specialized Centers of Nursing Research to include minority outreach as a part of their research efforts.

The task force meeting to discuss nursing research issues in relation to the special needs of minorities as well as American Indians and native Alaskans and Hawaiians which is planned for the Spring of 1990 is expected to define a framework for new directions of research on the health care problems of these populations, together with strategies for nurse scientists to seek solutions.

Research Training Initiative

As a relatively new research center within the NIH, the NCNR is responsible for a growing pool of investigators within an expanding area of science. Consequently, NCNR continues to place a strong emphasis on increasing the number of nursing research trainees. In 1989 NCNR supported 219 research trainees and 9 research career awards, thereby exceeding its goal of 227 total trainees for the second step of its multi-year research training initiative. The third step goal of 270 trainees and research career awardees for 1990 has been adjusted to 257, to conform to available funds. It is expected that this increase will serve to continue the needed growth in nurse scientists.

Research training for minority nurses remains a high priority for the NCNR in 1990. In November, a two day workshop on research and research training was convened to inform faculty of nursing schools, including those from Historically Black Colleges and Universities (HBCUs), about the extramural research and research training opportunities at NIH. NCNR anticipates the establishment of a mentor program in 1990 between NCNR scientists and HBCU schools of nursing to strengthen this effort.

On the recommendation of the National Advisory Council for Nursing Research, NCNR has also issued a program announcement to encourage research training applications and research career applications in Bioethics and Clinical Decision Making. This ongoing announcement emphasizes an interdisciplinary perspective to the preparation of scientists for this area of inquiry and an empirical approach to bioethical problems in clinical practice.

Caregiving and Alzheimer's Disease

The increasing age profile of the national population has focused growing attention on Alzheimer's Disease and other dementias, frailty and injuries among older persons, and the broader problems of family caregiving. In the development of the National Nursing Research Agenda, Priority Expert Panels (PEPs) for the two priority areas of Long Term Care and Symptom Management are defining and prioritizing nursing practice issues related to the care of Alzheimer's patients and formal and informal caregiving.

The Center has actively encouraged increased research and research training in this field of patient care. A program announcement was issued inviting applications for research training fellowships from qualified nurses specifically related to Alzheimer's Disease and related disorders. The Center also issued, in collaboration with other NIH Institutes, a program announcement and a request for applications (RFA) relevant to Alzheimer's Disease and related disorders, caregiving, and reducing frailty and injuries in older persons. In the past year NCNR awarded two supplements to

Alzheimer's Disease Research Centers of the National Institute on Aging to fund educational programs for providers of care to Alzheimer's patients. Two of the NCNR's new research centers focus on related patient care issues.

Some data suggest that informal caregivers (relatives, friends, or others who are not paid) experience extensive physical, emotional, and financial costs related to caregiving. One current project focuses on refinement and testing of a set of predictor variables intended to identify caregivers likely to deliver poor quality care or even to abuse the elderly patient. Factors that contribute to utilization of respite services by caregivers of the elderly are being addressed in another study. A third study in the preliminary stages of implementation will determine whether a Caregiver Support Program which encompasses preparation, advice, and support to caregivers will benefit the caregivers, their patients, and the families.

Other research projects NCNR is supporting that apply to formal and informal caregiving and long-term care of the elderly include: studies of rural home health care, continuity of care, and community support for the elderly following discharge from acute care settings. Additional projects are examining the impact of discharge planning by nurse specialists on such variables as the stress experienced by caregivers and the functional status of elderly patients with hip fractures.

Low Birthweight

Low birthweight (LBW) is a major cause of infant mortality in the United States and those low birthweight infants who survive represent 6.5 percent of live births annually. High morbidity due to chronic handicapping conditions such as cerebral palsy, respiratory and metabolic difficulties, blindness, mental retardation and learning disabilities is characteristic of those infants. Scientifically based nursing care can contribute to prevention of this condition as well as to the care of these infants and their families.

NCNR, in conjunction with the National Advisory Council on Nursing Research, has identified the issues surrounding LBW and its impact on infants and their families as a research area of the highest priority. It has begun a major initiative to increase nursing research in this field. Nursing research on LBW addresses four major areas of focus: preconception health, prenatal care, care of the LBW infant in the hospital, and follow-up care of the infant and the family after discharge.

Prenatal care should include identification of women who are at risk for premature labor and women who have a family history or personal experience with intrauterine growth retardation. Risk assessment should continue, in order to detect changes in status during pregnancy. Additionally, the social issue of access to prenatal care must be addressed and evaluated, especially among minority and low socio-economic status groups who are at high risk for poor pregnancy outcomes.

Among current NCNR projects in this area, one group of nurse scientists is testing the effectiveness of prenatal and post partum nurse home visitation as a means of enhancing the health and well-being of socially disadvantaged women and their first-born children. This study focuses on unwed, poor women and the beneficial effects of home visitation services and transportation during

pregnancy. A second study is developing and testing a social support intervention for low-income black income black women which is related to clinical outcomes of pregnancy, including LBW. Representatives from the black community will assist in developing culturally appropriate interventions.

Methods of caring for LBW infants in neonatal intensive care nurseries are another area of study supported by the NCNR. Physical care of these infants such as feeding, respiratory care, skin care, and physical positioning needs further basic and clinical research attention, to identify optimal care practices during hospitalization and after discharge. NCNR has issued a program announcement, in collaboration with the National Institute of Child Health and Human Development, inviting applications to study optimal physical care practices for hospitalized LBW infants.

Pressure Sores

Pressure sores are a source of considerable human suffering, a financial burden to families and health care institutions, and a significant clinical problem in patient care. Although the precise incidence is unknown, the prevalence of pressure sores reportedly ranges between 3 and 14 percent among hospitalized patients, and between 15 and 25 percent among patients admitted to skilled nursing facilities. Increasing prevalence of pressure sores is predicted due to increasing numbers of fragile elderly and survivors of serious trauma. Lack of research to support the scientific management of pressure sores hinders both their prevention and treatment.

To date, little is known about the natural history of the development of pressure sores, the stages of clinical lesions, and effectiveness of the numerous treatment modalities appropriate for the various populations afflicted. NCNR continues to encourage research addressing these issues specifically for pressure sores, and more broadly, as they relate to general skin integrity. There is a need for scientifically derived data to guide nurses in clinical and home care settings to develop effective skin care programs applicable to the needs of individual patients.

NCNR supports several investigators studying the prevention and treatment of pressure sores among populations of various ages and in diverse settings. The aim of one research project is to validate a scale for predicting the risk of developing pressure sores among home care, hospitalized and nursing home patients. Previous scales have tended to over predict which patients would develop pressure sores and to misclassify as "not-at-risk" patients who subsequently developed pressure sores. When further refined, the scale is intended for use by health care providers and by family members who need to determine at what point preventive measures are needed.

A second project is assessing the effectiveness of transcutaneous electrical nerve stimulation (TENS) in the healing of pressure sores. Until recently, there had been no known means of enhancing blood supply to tissues by direct stimulation of cutaneous vasodilation. Recently, the application of TENS demonstrated a marked and prolonged cutaneous vasodilation in patients diagnosed as having Raynaud's Disease or diabetic polyneuropathy. In the current investigation, subjects with resistant decubitus ulcers are being randomly assigned to one of two treatment regimens: conventional treatment or

conventional treatment combined with TENS, and differences in the rate of healing between these two approaches will be determined.

In its development of a National Nursing Research Agenda, NCNR has identified symptom management and long term care for the elderly as two priority areas for increased emphasis in nursing science. The maintenance of skin integrity is vital in both areas and a serious clinical problem for nursing practice.

In March 1989 the National Pressure Ulcer Advisory Panel, a private organization of health care professionals committed to the prevention of pressure sores, convened a conference of multidisciplinary professionals, in which NCNR participated, to assess the state of scientific knowledge on this topic. After hearing expert testimony and considering the evidence of accumulated research, the panel concluded that there is a need for a major research initiative into pressure sores due to the paucity of reliable data. NCNR will continue its support of research in this area.

Behavioral Research

Behavioral research related to health is an important part of the mandate of the National Center for Nursing Research, and accounted for over one quarter of Center-supported research and training in 1989. Although NCNR is a small part of the NIH, the Center supported 7 percent of all the behavioral research supported by the NIH in the latest year for which figures are available. Within its mission to support basic and clinical nursing research that impacts on patient care, NCNR supports research on the behavior of patients and care providers related to health and illness. NCNR is especially interested in the development and maintenance of health promoting behaviors and the measurement of positive outcomes correlated to those behaviors. Examples of behavioral research currently being supported are the general areas of recovery from illness, parenting, health promotion and disease prevention.

Behavior and lifestyle are major factors in each individual's reaction to an illness and the subsequent course of recovery. Three major areas under study are recovery from cardiovascular illness, coping with cancer treatment, and management of chronic diseases. Recovery patterns of older women after myocardial infarction are being examined to determine how to assist these women in returning to maximal functioning. Patients who have undergone cardiac surgery are being studied to identify coping behaviors following surgery and to determine the effects of behavioral interventions. Behaviors and strategies for coping with cancer and its treatment are being tested, and may assist the patient in minimizing the unpleasant and sometimes debilitating side effects of treatment. Behavioral management of chronic disease and associated conditions are being studied, with currently funded research related to diabetes mellitus, asthma, depression, osteoporosis, hip fracture, urinary incontinence, and obesity.

Parenting is a challenge with healthy children. When the task is compounded by illness or disability, specific coping behaviors are often needed. Current studies of the NCNR address parental behaviors useful with children who are profoundly deaf as well as with infants with colic.

The NCNR supports a number of research studies in the field of health promotion and disease prevention. Identification of fundamental psychosocial

mechanisms and strategies to influence lifestyle choices that underlie the maintenance of healthy behaviors are being studied in populations of adolescents, pregnant women, and middle aged adults. Prevention and early detection of cancer through breast self-examination is a continuing emphasis in health care and is supported as a research interest of the Center. Two additional areas of behavioral research at NCNR are research on the prevention of HIV infection, and the prevention of low birthweight and its complications. Program announcements have been issued in both of these areas and studies are currently being supported.

Rural Health

The adequacy of health care in rural areas is a growing concern of the Nation. As wealth and services of all types become more concentrated in the nation's urban and suburban areas, the Congress has come to realize that many of the advancements in medical care are slow to come to the public in rural areas, or are unavailable altogether. The role of nurses in health care in rural areas differs from that in urban areas because of the increased need for visiting services to homes, small clinics and remote facilities, and the decreased availability of physicians.

As a result, the Congress has encouraged the NIH to increase support for research on rural health care, in particular those aspects of nursing research related to rural areas. The NCNR will devote additional resources in 1990 and 1991 to research that may assist nurses in practice in rural areas. NCNR is also emphasizing research that focuses on clinical and basic science by exploring the underlying reasons for differences in morbidity and mortality between rural and non-rural populations.

The NCNR is also funding a study to test approaches for reducing the risk of cardiovascular disease in school age children in rural North Carolina. The NCNR is also funding a study of home care, continuity of care and community support for older adults in a rural area of Colorado, to determine the extent of existing services provided and their accessibility.

The NCNR is supporting two cooperative agreements with the Division of Nursing to test innovative practice models for nurses practicising in acute care hospitals. Each study includes rural hospitals and it is expected that valuable information will be provided for nurses practicing in rural areas. It appears that nurses in rural areas provide a broad array of services, usually have more general than specialized roles, and frequently perform under staffing shortages. The studies will investigate new approaches to clinical decision making, organization of nursing practice, compensation and other issues related to retention, and will link nursing resources to measures of quality and outcomes of care.

The NCNR is planning a special task force meeting during the Spring of 1990 to discuss nursing research issues in relation to the special needs of American Indians and native Alaskans and Hawaiians. The health care problems of these populations are attributable, in part, to the decreased availability and quality of health services in rural areas, in addition to culturally-based issues or perspectives affecting health care utilization among these populations.

Rehabilitation Research

NCNR currently supports rehabilitation research addressing a number of prevalent and disabling conditions, including diseases of the cardiovascular system, stroke, and disabilities associated with hip fractures. Planning for the Center's future program activities indicates that opportunities for fruitful research lie in the fields of restoration of functional abilities following neurological trauma, psychological impact of chronic disease, and functioning associated with disease and disability among older persons.

Cardiovascular rehabilitation research supported by the Center focuses on the quality of life following cardiac surgery and the restoration of functioning of the individual following myocardial infarction. Research has been prompted by clinical problems confronted by nurses while helping patients and their families through cardiac transplantation as well as the adjustment and recovery from a heart attack.

NCNR also supports research addressing problems associated with neurological trauma and cognitive deficits. One investigation addresses the impact of an aerobic training program on the physiologic and psychological well-being of stroke patients. Another investigation focuses on depression in stroke patients, and its relationship to the site of the lesion and the length of time since the stroke.

NCNR has also collaborated with other NIH institutes in activities related to medical rehabilitation research. In response to the release of the Interagency Head Injury Task Force Report, NCNR and the National Institute of Neurological Disorders and Stroke have discussed opportunities to address research areas of mutual concern. NCNR collaborated with the National Institute on Aging on an RFA entitled "Reducing Frailty and Injuries in older Persons". NCNR and NIA also continued their collaborative efforts in urinary incontinence research, another disability which disproportionately affects older persons and requires rehabilitative measures.

Effectiveness of Patient Care

Congress has indicated that the Agency for Health Care Policy and Research should collaborate with NCNR concerning the new agency's newly mandated Medical Treatment Effectiveness Program. More specifically, Congressional report language states that the program should include non-physician health care providers, particularly for rural areas where such providers predominate.

In implementing its mission of patient care research the NCNR has emphasized the importance of quality of care and patient outcomes in its clinical research programs. From the care delivery research perspective, there are multiple influences that directly affect the outcomes of patient care. Among these are the patient's own behavior, family member involvement in care, the actions of physicians and nurses, and other provider factors.

Cumulative research findings have indicated that there are unanswered questions about which medical treatments lead to improved patient outcomes, versus no improvement or a worsening of the underlying condition, how treatments effect patients' quality of life, and which are the most appropriate surgical procedures for certain patient conditions. Selecting

diagnoses or procedures for study which have a high variation in care and high variation in outcomes, and for which data are available for study, may be the best path to important advances.

The initial activities of the effectiveness of medical care initiative will be limited to outcomes of care that occur in hospitals. Because both physicians and nurses have great influence over patient care delivery in hospitals, it is often impossible to differentiate the outcomes of medical practice from nursing practice without research. NCNR plans to hold a conference during FY 1990 to determine research strategies and methods to validate the influence of nursing practice on patient care outcomes as differentiated from other influences, and will continue to support research and research training examining the quality and outcomes of patient care.

Bioethical Concerns in Patient Care

National attention has increasingly focused on ethical issues arising during patient care which are encountered by patients, their families and health care providers. NCNR staff, in conjunction with the National Advisory Council for Nursing Research, has developed the basis for an Extramural Program in Bioethics and Clinical Practice Research which will initially focus on studies that examine issues in clinical decision making. NCNR conducted a workshop in January 1989 that brought together experts in bioethics and clinical practice research to discuss strategies for increasing the numbers of scientists active in the empirical study of clinical ethical issues and to make recommendations for research.

NCNR has also published two program announcements indicating the interest of NCNR in research and research training focused on bioethics and clinical decision making involving all patient populations and health care settings. The research effort will initially be limited to small grants so as to enable the development of a base of empirical and methodological studies for future larger scale studies. The research training effort will include the usual NCNR training mechanisms, and particularly, will provide a mechanism for established clinical investigators to add this new dimension to their work.

Nursing Resources and Quality of Patient Care

The factors contributing to shortages of qualified nurses in some sectors of the health care industry are quite complex and do not lend themselves to simple solutions. Such shortages and instances of high turnover among nursing staff are of great concern to all persons associated with health care, particularly the recipients of care.

A current study addresses the effectiveness of a Professional Practice Contract Model in a large tertiary hospital. Variations of use of the practice model among different nursing units will be studied, and units employing the model will be compared with units not using it, in terms of the quality and cost of patient care, patient satisfaction, the nurses' job satisfaction, absenteeism and turnover. Another study supported by the NCNR employs a leadership building intervention within nursing departments in four large urban hospitals. The effect of this intervention on retention of the nursing staff will be measured, as well as on the safety and satisfaction of the patients.

It is hoped that these and the many other studies supported by the NCNR in this field will foster new approaches to practice in clinical settings, and lead to enhanced patient care and professional satisfaction among nurses.

National Center for Nursing Research

Intramural Research

1991 Authorization: Indefinite

Budget Authority:

1990 Appropriation		1991 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA
---	$202,000	2	$266,000	+2	+$64,000

Purpose and Method of Operations

In 1990, the National Center for Nursing Research initiated an intramural research program on the NIH campus in Bethesda, Maryland. NCNR's initial intramural research efforts are targeted to individuals infected with the Human Immunodeficiency Virus (and their partners and families) who are currently participating in studies conducted at the NIH Clinical Center by intramural investigators of the National Institute of Allergy and Infectious Diseases. The primary purposes of the program are to:

develop and conduct basic and clinical research that contributes scientific knowledge pertinent to nursing practice and health care of individuals with HIV infection;

provide training opportunities for nurse scientists in the field of HIV infection;

disseminate research findings, and translate those findings into nursing practice and health care delivery to individuals with HIV infection.

Within the NCNR's national planning effort to define a National Nursing Research Agenda, a Priority Expert Panel highlighted five areas for HIV nursing research. Three of the five identified priority areas -- physiological aspects of nursing management, psychological aspects of nursing management, and applied clinical ethics -- are particularly amenable to clinical research efforts within the NIH intramural environment.

The general aim of NCNR's Collaborative Intramural Program for HIV Infection is to conduct an organized program of research that will increase our understanding of, as well as develop interventions for, health problems that are particularly prevalent among or troublesome to individuals infected with HIV, their families, or caregivers. The ultimate goal of this research effort is to minimize dysfunction and suffering due to physical or psychosocial sequelae of HIV infection, such as unintentional weight loss, decreased appetite, or other nutritional disorders; diarrhea; fatigue; oral complications; pain; or dementia. Other common problems such as anxiety, depression, loss and grieving, and quality of life may also be addressed.

Especially while HIV infection remains incurable, it is important to direct efforts towards discovering ways to decrease morbidity in order to maximize the quality of an individual's life and to diminish the cost, both economic and personal, resulting from HIV infection and its treatment. This becomes even more important because HIV infected individuals are living longer due to advances in disease therapy, resulting in a prolonged chronic condition rather than a rapidly terminal illness.

By collaborating with the NIAID and the Clinical Center, NCNR intramural investigators will maximally and efficiently use valuable NIH resources, such as patient care services and office space; clinical, biophysiologic, and psychosocial patient information; and scientific and research support personnel. Most NCNR studies will collect new data concurrently with other NIAID clinical studies, while some NCNR studies will utilize existing data to address specific additional research questions.

Rationale for the Budget Request

The 1991 request for intramural research is $266,000, an increase of $64,000 over 1990.

National Center for Nursing Research

Research Management and Support

1990 Authorization: Indefinite

Budget Authority:

1990 Appropriation		1991 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA
30	$2,799,000	35	$3,082,000	+5	+$283,000

Purpose and Method of Operations

This activity provides salary support and other expenses associated with the professional and administrative staff of the Center, including the Office of the Director, the Office of Administrative Management, and the Division of Extramural Programs.

The Office of the Director (OD) provides overall guidance and professional leadership to carry out the extramural and intramural programs of the NCNR. Its functions also include planning and evaluation, information and public affairs, legislative liaison, staff support to and liaison with the National Advisory Council for Nursing Research, and liaison with other nursing organizations within and outside the federal government.

The Office of Administrative Management performs a variety of functions including financial management, personnel management, grants management, administrative services to all components of the Center, and coordination with other offices and organizations within the NIH.

The Extramural Program staff of NCNR's three major research areas -- Acute and Chronic Illness, Nursing Systems, Health Promotion and Disease Prevention -- provide the scientific support and consultation required for processing the research and research training applications and monitoring the awards of the NCNR, coordinate and plan scientific initiatives, manage the peer review process for all competing research training and career development applications, and compile and report scientific information relevant to NCNR's programs.

Rationale for the Budget Request

The 1991 request for research management and support is $3,082,000, an increase of $283,000 over 1990.

NATIONAL INSTITUTES OF HEALTH

National Center for Nursing Research

Detail of Permanent Positions

	FY89 Actual	FY90 Estimate	FY91 Estimate
ES3	1	1	1
Subtotal	1	1	1
GS/GM-15	2	2	2
GS/GM-14	5	6	6
GS/GM-13	7	8	9
GS-12	4	5	6
GS-11	0	1	2
GS-10	1	1	1
GS-9	2	3	4
GS-7	4	5	5
GS-6	1	1	1
GS-4	1	1	1
Subtotal	27	33	37
Total permanent positions	28	34	38

NATIONAL INSTITUTES OF HEALTH

National Center for Nursing Research

New Positions Requested

		1991	
NCNR Intramural Research	Grade	Number	Annual Salary
Nurse Scientist	GS-13	1	$44,021
Research Assistant	GS-11	1	30,887
NCNR Research Management and Support			
Program Analyst	GS-12	1	37,019
Computer Specialist	GS-11	1	30,887

NATIONAL INSTITUTES OF HEALTH

National Center for Nursing Research

Advisory and Assistance Services

The category of Personnel Appointments will be increasing from $13,000 in 1989 to about 22,000 in 1991, with most of the increase occurring in 1990. The number of members on the National Advisory Council for Nursing Research is increasing from 12 to 15 members.

Another reason for the increasing cost of the Personnel Appointments category, as well as the increase in Studies, Analyses, and Evaluations is the growing national research planning effort to develop the National Nursing Research Agenda. NACNR members are participating in the work of the Priority Expert Panels, and outside experts are brought in to evaluate our research portfolio, in the context of national nursing research needs in specific fields.

Management and Professional Support Services will increase due to the cost of an Intramural Program consultant, whose skills are needed to effect the establishment of a new Collaborative Intramural Research Program.

Internal Controls

The NCNR Budget Office, in consultation with the Executive Officer, prepares an annual consulting services plan, outlining needs for various consulting services, utilizing the guidance and definitions in DHHS General Administration Manual (GAM) chapter 8-15, Advisory and Assistance Services. As the need for teach consultant arises during the year, the program official or staff member involved prepares a Purchase Request explaining the services needed and reasons that the services cannot be performed by staff. The requester also contacts three sources capable of providing the required service, in order to choose the least expensive one.

Review of each request is performed by the Director of the Office or the Director of Extramural Programs as appropriate, and by the Budget Assistant for conformance to GAM 8-15. The Executive Officer makes the decision for approval or disapproval, and involves the NCNR Director if necessary. The Administrative Assistant processes the approved orders.

TUESDAY, MARCH 20, 1990.

NATIONAL CENTER FOR HUMAN GENOME RESEARCH

WITNESSES

DR. JAMES D. WATSON, DIRECTOR, NATIONAL CENTER FOR HUMAN GENOME RESEARCH
DR. WILLIAM F. RAUB, ACTING DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. ELKE JORDAN, DEPUTY DIRECTOR, NATIONAL CENTER FOR HUMAN GENOME RESEARCH
DR. MARK S. GUYER, ASSISTANT DIRECTOR FOR PROGRAM COORDINATION, NATIONAL CENTER FOR HUMAN GENOME RESEARCH
JAMES C. VENNETTI, EXECUTIVE OFFICER, NATIONAL CENTER FOR HUMAN GENOME RESEARCH
ERIN S. BURGESS, BUDGET OFFICER, NATIONAL CENTER FOR HUMAN GENOME RESEARCH
DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DEPARTMENT OF HEALTH AND HUMAN SERVICES

INTRODUCTION

Mr. NATCHER. We have before the committee at this time Dr. Watson, the Director of the National Center for Human Genome Research.

Dr. Watson, it is a pleasure to have you back before the committee, and before you give us your statement, tell us who you have with you there at the table.

Dr. WATSON. Yes. I have several members of the National Center for Human Genome Research. On my extreme left is Dr. Mark Guyer, the Assistant Director for Program Coordination. Next to him is James Vennetti, the Executive Officer, on my closest left is Erin Burgess, my Budget Officer, and on my right is Dr. Elke Jordan, the Deputy Director.

Mr. NATCHER. Thank you very much.

Now, Doctor, we will be pleased to hear from you.

Dr. WATSON. I have a formal statement which has been prepared for the record.

Mr. NATCHER. It will be placed in the record in its entirety.

Dr. WATSON. I will try to make some informal remarks about the center.

ESTABLISHMENT OF THE CENTER

This was a very important year for the center because this is its first year. We came into existence on October 1, 1989 and we are moving ahead very fast.

The coming into existence of the center was a very well-thought-out effort. It reflected much discussion over the previous 5 years, in particular discussions within prestigious committees of the Nation-

al Academy of Sciences and of the Office of Technology Assessment, both of which strongly urged the establishment of a human genome program with a budget of approximately $200 million a year and to last 15 years so that the total final expenditure of the program would be approximately $3 billion.

PURPOSE OF THE HUMAN GENOME PROJECT

The aim of the program is to completely identify the genes of a human being and to tell us what we are made of genetically. It is not a complete end in itself because once we know the genetic material, we will have much to do to study it afterwards. It will be an enormous resource towards understanding both why we are healthy and why we may be diseased.

Launching the Human Genome Project reflects the fact that more and more we realize there are defects in our genes which are responsible for many of our diseases. Not only a series of minor diseases but major diseases like diabetes, coronary artery disease, and cancer, all have predispositions related to the exact genes that we carry.

In trying to understand disease at the genetic level, we have to isolate the genes, which means we first have to know where they are on the chromosome. We have to map these genes. Once we have located them, we want to isolate them, so that we can study exactly what they do.

There has been an enormous triumph this past year in first mapping and then isolating the gene for cystic fibrosis. This triumph will enable us to really study the biochemistry or the molecular basis of the disease.

There are many diseases still out there where we want to isolate and study the gene. The finding of the cystic fibrosis gene was an immense effort, culminating roughly 20 years of work. It came to success due to the funds available, but even more because of the very intelligent people who were carrying out this research.

What the National Center for Human Genome Research has done over this past year is to prepare a plan for the next 5 years. This is a joint plan between the National Institutes of Health and the Department of Energy, who, as you know, are the two agencies supporting this work. We have established a joint advisory subcommittee, and that joint advisory subcommittee now has joint working groups, and I am very pleased to say that the relationship between the DOE and the NIH is extremely good. We see no complications.

We are going to Salt Lake City on Wednesday for a joint linkage mapping meeting and then moving on to Los Alamos for a joint physical mapping meeting. We are working together. Many people thought there might be competition between the two agencies, but I can happily say that is not going to be the case. If there is competition, it is healthy competition. We are working very well together.

The immediate objective of the next 5 years is to develop the map and to roughly find where genes are located. Once we have developed the map, we want to work out the structures of these genes, by sequencing the base pairs. For these 5 years we will con-

centrate on mapping. That is the course the National Academy of Science said we should follow and that is exactly what we are doing.

Also, what we are doing in this first 5 years is to reduce the cost of sequencing the DNA to a manageable level. It now costs roughly $5 a unit to sequence. That is far too expensive if we are going to do the whole genome. We want to reduce that cost by at least a factor of 10, to roughly 50 cents. I think we can do it in 5 years. We do not intend to start large-scale sequencing until we have reached the point where we know it is economically feasible.

PURPOSE OF THE HUMAN GENOME PROJECT

The third objective of our program is to set up a serious discussion of the ethical implications of this genetic image so that when the genetic image comes out, society will be ready. We have appointed an excellent committee of citizens to our Ethics Working Group, and I think we should say this committee reflects society as distinct from the scientists.

We are really trying in this working group to appoint people who are going to be the recipients of this knowledge and see what they want to do. We have said that we want to spend at least 3 percent of the money of the program on ethics, and with time, it would not surprise me that we will find that we should spend more.

Three percent is not an upper limit. I think society justly wants that. We know the good that will come from the program, but there could be complications, and we want to consider these areas at the very beginning. I think the ethics program will be a very good and important one.

Let me make just one last point. I think there is some misunderstanding that we are doing this process sort of from A to Z; that we are just mapping randomly and then we are going to sequence. In fact, the first mapping we are doing is disease oriented.

We really want to do things which would bring benefits as soon as possible to the public. We are very health oriented.

The Human Genome Project is just not a super project where our fun is having the super project. We think this is a very important mission of the National Institutes of Health.

My whole career has been devoted to genetics. Of course, I have been very pleased at seeing its successes in understanding disease and, over the past 20 years in particular, I have seen the success in understanding cancer through our ability to isolate the genes that cause cancer.

In the case of cancer, we used viruses to get the genes. In the case of many other diseases, we cannot. We have to have the program which the center is now proposing to give us a realistic chance of getting the genes. I think it is the mission of the National Institutes of Health to find these genes.

I am really very pleased that I have been asked to head the center. I can't think of a more important task and I will devote all my resources to seeing that we succeed.

[The information follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Center for Human Genome Research

Mr. Chairman, and members of the subcommittee, it is my pleasure to appear before you today for the first time as director of the newly established National Center for Human Genome Research. Our mission is to lead the NIH component of the worldwide research effort now popularly called "the human genome project." Being before this subcommittee today is particularly significant because the budget for genome research has reached a level from which we can formally launch the 15-year human genome project. The goal of this endeavour is to determine the order, or sequence, of the subunits of human DNA, the substance that makes up our genes. Doing so will allow us to identify and locate all the genes that comprise the human genome. The task is both tremendously important and formidable.

Recognizing the growing role the National Institutes of Health has played in the human genome project, Secretary Sullivan formally established the NIH National Center for Human Genome Research in October of 1989. Before that time, our business was conducted as part of the NIH director's office, where we were called the Office for Human Genome Research.

We have watched the human genome project be transformed from an ambitious idea--some said overly ambitious--into a reality. In the past year, we have developed a broad and orderly approach to tackling the many and diverse challenges surrounding the genome project. Deciphering the genetic information encoded within our DNA will provide an important handbook to explain how we function as healthy human beings. It will also provide us with a new understanding of the genetic components of such widespread illnesses as heart disease, high blood pressure, diabetes, and many, if not all, cancers. As we enter the last decade of this century, we are ready to proceed with a project that will have a profound impact on the biological science of the next century.

Locating individual genes on a chromosome and then analyzing the DNA components that make up these genes is now possible for increasingly complex genomes. The National Institutes of Health has supported much of the basic research that has brought us to this threshold, particularly research emanating from the invention of recombinant DNA technology in the early 1970s. Because of the generous funding provided by the Congress to the National Institutes of Health, the United States is clearly a leader in the science of gene mapping and sequencing.

How will we use this scientific leadership to achieve our goal? This past August, advisors to the National Institutes of Health and the Department of Energy met to plan our collective mission over the next 5 years of this project. The scientific experiences of our respective agencies dovetail remarkably and bring complementary strengths to the human genome project. After vigorous planning and coordination, our path is now well charted and A Five-Year Plan for

the Human Genome Project was issued. Briefly, the goals we have established for fiscal years 1991 through 1995 are: 1) to map in detail the human genome, both genetically and physically; 2) to improve the efficiency of DNA sequencing methods to reduce the cost to an acceptable level; 3) to map and in some cases begin to sequence the genomes of selected model organisms; 4) to develop computer and other information technology for storing and analyzing map sequence data; 5) to identify and examine ahead of time the ethical, legal and social issues raised by the availability of genetic information and develop policy options to address them; 6) to train researchers in the combined areas of scientific expertise needed to map and sequence the human genome and to interpret the resulting information; 7) to support innovative technology development as well as improvements in current technology to meet the needs of the human genome project; and 8) to transfer technology invented as part of the human genome project to U.S. industries for development into useful commodities that will improve the quality of life for Americans and compete favorably in the international marketplace.

As part of the August planning meeting, we evaluated the state of the science of gene mapping and sequencing. We were excited by the rapid progress that has taken place over the past two years. In that time, many promising gains have been made in the technology of mapping and sequencing. Mapping refers to identifying the location of genetic or physical landmarks on chromosomes. The so-called "physical" map of the human genome uses nucleotides, the chemical subunits of DNA, as its unit of measure. Over the years, many different, and often exclusive, methods have been developed for determining nucleotide distances between recognizable landmarks, such as genes. On the one hand, these diverse methods have allowed scientists to make great strides in fashioning physical maps. On the other, they have made comparing information in maps produced by different methods very difficult, if not impossible. This past summer, four genome scientists proposed a system that promises to be the "Rosetta Stone" for physical maps. This system uses markers called "sequence-tagged sites," or STSs, that can be incorporated into any mapping technique used today. Scientists working in different laboratories, using different techniques, can now add their results to a common physical map that will be available to and usable by all genome researchers. The properties of STSs will allow scientists to use them to regenerate any desired piece of DNA in their own laboratories--an advantage that will reduce dependence on centrally stored DNA pieces.

During fiscal year 1990 we are developing and refining the STS idea. Our advisory council has established a joint working group with the DOE to discuss the establishment of a pilot program for converting existing markers to the STS system and for a central computer database for STS information. We hope to begin this program in 1991.

Another hurdle physical mappers have faced is finding ways to isolate and reproduce long segments of human DNA for analysis. Recently, Dr. David Schlessinger, at Washington University in St. Louis, used modified yeast chromosomes to isolate and clone several overlapping segments of human DNA from the X chromosome. In all,

these segments spanned a stretch 2 million nucleotides long. This achievement, which has produced the longest continuous region of human DNA ever cloned, greatly advances our efforts to produce a complete physical map because it demonstrates that our 5 year goals for physical mapping are indeed achievable.

Usually, genes located near each other are passed on together in a "linked" way to the next generation. Maps called genetic "linkage" maps, designed to track disease genes from one generation to the next, rely on knowing the location of easily identifiable genetic markers that are routinely passed along with specific disease genes. Finding enough of such markers on all the human chromosomes will streamline our research efforts and help other efforts to isolate and analyze disease genes. NCHGR grantees have played a key role in adding landmarks to the current genetic linkage map. Dr. Helen Donis-Keller of Washington University in St. Louis, has been working to narrow the gaps between markers. Dr. Raymond White, at the University of Utah, is focusing on regions of the map that contain few markers. As part of his project, Dr. White is also developing markers that can be translated usefully to the physical chromosome map.

Several grantees are looking for new types of linkage markers that will allow gaps to be filled and mapping to be done more easily, perhaps even by automation. One example is the "CA repeat," a new type of marker developed by a number of scientists, including Dr. James Weber at the Marshfield Medical Research Foundation in Wisconsin. The number of CA repeats at a given site in DNA can be used as a genetic marker because it differs from person to person and can be analyzed using the powerful new polymerase chain reaction to trace its inheritance from one generation to the next.

Sequencing all of the 3 billion nucleotides in human DNA is the human genome project's ultimate goal. Recently, the NCHGR supported a major conference at Wolf Trap, Virginia, to bring biologists doing DNA sequencing together with technology experts to discuss the state of the science of sequencing large pieces of DNA. We are encouraged by the consensus of the many top-notch scientists at that first Genome Sequencing Conference: sequencing technology is improving; the automated DNA sequencers are reliable and useful for sequencing large DNA stretches.

However, these are first-generation machines. The time, labor, and expense even these machines now require dictate that significant improvements in DNA sequencing methods are still required before we can completely sequence human DNA. Dr. Leroy Hood, at the California Institute of Technology, for example, has used machines to sequence a stretch of human DNA 70,000 nucleotides long, in about 7 months. With continued improvements in these machines, in the associated computer programs and in automation of other steps in the sequencing process, Dr. Hood expects to increase the capability of automated sequencing to about 50,000 nucleotides per week. We are also supporting research and development of entirely new approaches to sequencing, realizing that the best technology for this job may not yet have been invented.

To assure that mapping and sequencing technology development moves as rapidly as possible, we plan to continue sponsoring a variety of conferences and workshops. The next sequencing conference, for example, is set for the end of this year in South Carolina.

Mapping and sequencing the human genome demands the coordinated, labor-intensive efforts of specialists in a variety of scientific fields. Foremost among our initiatives is the establishment of multidisciplinary genome research centers. Housing experts in genetics, molecular biology, as well as in computer science and even physics, these centers will serve as the centerpiece of the genome project and will offer resources and collaboration and technology transfer opportunities to all genome researchers. In fiscal year 1990, we expect to fund three of these centers. In 1991, we hope to fund 9 and plan to fund up to 20 in the next few years.

While the knowledge gained from genome information will undoubtedly lead to many health benefits, we recognize the many concerns that possession of such information may pose. The joint NIH-DOE ethics working group, chaired by Dr. Nancy Wexler at Columbia University, has made significant progress in focusing our program on the social, ethical, and legal issues raised by the availability of genetic information. About 3 percent of the NCHGR budget will go toward this research. We have already received a number of grant applications to study these very important issues, and hope to fund many more grants in fiscal year 1991. In 1991, we also plan to begin "town meetings" around the country to educate the public about this program and to seek their input on these matters.

Mr. Chairman, I have been enthusiastic about the human genome project from the time the idea was born. But I could not have predicted then that it would take such positive shape as quickly as it has in these past 2 years. If our short history is an example, I have every confidence that our future will be productive and promising.

The budget request for the National Center for Human Genome Research for fiscal year 1991 is $108,029,000. I will be happy to answer your questions.

CURRICULUM VITAE

Name James Dewey Watson

Birthdate. April 6, 1928 - Chicago, Illinois

Education: 1947 - B.S., Zoology, University of Chicago
1950 - Ph.D., Zoology, Indiana University

Professional Career:

1950-51	Research at the University of Copenhagen with H. M. Kalckar
1951-52	Research at Cambridge University in the Cavendish Laboratory
1953-55	Senior Research Fellow in Biology, California Institute of Technology
1955-56	Research at Cambridge University in the Cavendish Laboratory
1956-58	Assistant Professor of Biology, Harvard University
1958-61	Associate Professor of Biology, Harvard University
1961-76	Professor of Biology, Harvard University
1968-	Director of the Cold Spring Harbor Laboratory
1988-89	Associate Director for Human Genome Research, NIH
1989-	Director, National Center for Human Genome Research, NIH

Awards:
The John Collins Warren Prize of the Massachusetts General Hospital (with F.H.C. Crick), 1959
Eli Lilly Award in Biochemistry, 1960
Albert Lasker Prize (awarded by the American Public Health Association), 1960
Research Corporation Prize (with F.H.C. Crick), 1962
Nobel Prize in Medicine (with F.H.C. Crick and M.H.F. Wilkins), 1962
John J. Carty Gold Medal of the National Academy of Sciences, 1971
The Presidential Medal of Freedom, 1977

Honorary Degrees:

D.Sc., University of Chicago, 1961
D.Sc., Indiana University, 1963
L.L.D., Notre Dame University, 1965
D.Sc., Long Island University (C.W.Post), 1970
D.Sc., Adelphi University, 1972
D.Sc., Brandeis University, 1973
D.Sc., Albert Einstein College of Medicine, 1974
D.Sc., Hofstra University, 1976
D.Sc., Harvard University, 1978
D.Sc., Rockefeller University, 1980
D.Sc., Clarkson College, 1981
D.Sc., State Univ. of New York, Farmingdale 1983
M.D., Buenos Aires, Argentina, 1986

Professional Affiliations:

American Society of Biological Chemists
American Association for Cancer Research

Honorary Affiliations:

American Academy of Arts and Sciences (1958)
National Academy of Sciences (1962)
Danish Academy of Arts and Sciences (1963)
Honorary Fellow, Clare College, Cambridge University (1968)
American Philosophical Society (1977)
Atheneum (London) (1980)
Royal Society (London) (1981)

FIVE-YEAR PLAN FOR THE PROJECT

Mr. NATCHER. Dr. Watson, thank you very much.

You probably were here—if not, I know our friend Dr. Raub was here—when I explained to those present that if they asked me to place a man on the cover of Time magazine for "Man of the Decade," I would have chosen, instead of Mr. Gorbachev, one of you people in health or education. I say that to you frankly.

Dr. Watson, we are glad to have you before our committee.

Last year this committee requested a comprehensive spending plan for the genome project. The report that we received laid out specific plans for the next 5 years, but it did not provide any updates to early estimates of the cost of the project.

Can you give us some idea now, Dr. Watson, as to the cost?

Dr. WATSON. In the 5-year plan we did want to estimate costs, but when we pass it through the bureaucracies, OMB doesn't really like us to say anything about 3 to 5 years down the line. However, we have a very informal, unofficial fiscal plan for the program for the next 5 years with the costs that we would put with the project. I always like to put down figures, because I think if you don't do estimates, you are not thinking, but just expressing wishes.

Mr. NATCHER. Dr. Watson, can you give us just a general idea.

Dr. WATSON. The general idea is that in this year's Federal budget, the White House has requested that we receive $108 million. For next year we would like to come up to full steam, which would be $133 million. That is assuming that the Department of Energy is carrying one-third of the costs and we are carrying the other two-thirds. The final request to this committee would be $133 million, and that would be inflation adjusted in subsequent years.

When the National Academy of Science made their report 3 years ago, they said the total project should cost $200 million per year. We think in the past few years we have seen reasons why the project can, in fact, be done cheaper.

We haven't put an inflation adjustment in saying it was $200 million 3 years ago and now the program should be about $240 million. We think it should be $200 as of today or $200 as of October 1 of fiscal year 1992.

COST OF THE ENTIRE PROJECT

Mr. NATCHER. Dr. Watson, generally speaking, as far as using the figure of $200 million, do you feel that this is a good, sound figure?

Dr. WATSON. When we get together 15 years from now, I trust it is going to be less than that.

DEVELOPING THE BUDGET

Mr. NATCHER. Now, Dr. Raub, what kind of scrutiny has the genome project received in the NIH internal budget process?

Dr. RAUB. It occurs at two levels, Mr. Chairman. First, preparatory to the general budget discussions, there is a chartered advisory committee that provides advice and guidance to Dr. Watson and his colleagues, including the interactions with the Department of

Energy that sets the overall framework for the priorities. From that the budget requests are derived.

As the budget is developed, as for the other institutes, the center is invited to present everything from its professional judgment budget through alternatives within various other budget levels. These are then reviewed by the NIH director and senior staff, and an overall NIH budget is developed. We then defend that through the higher levels of the administration.

Mr. NATCHER. Dr. Raub, just speaking as one Member of the committee, I certainly believe this is a proposal and a project that should be followed rather carefully as far as NIH is concerned; the genome program generally is accepted, believed in and supported, isn't that right, Dr. Raub?

Dr. RAUB. Yes, sir, it is. It is one of the highest priorities for the National Institutes of Health.

FUNDING MECHANISMS

Mr. NATCHER. Dr. Watson, how do you expect to allocate funding among research mechanisms in the next few years?

Dr. WATSON. Virtually all our money as we have started up the program has gone out through R-01 research grants. Essentially it is grants to individuals to do pilot projects which will tell us what are the most efficient ways to finalize the project.

Over the next 5 years we will have two main emphases. We will continue the grants to single investigators at approximately 50 percent of the total budget. We then want to build up to about 35 percent or 40 percent of our budget funding research centers in academic institutions and possibly within major industrial companies, where we will finalize the maps, come out with a high resolution map, and then begin sequencing.

We see that for the project to be done with an acceptable cost, within an acceptable time period, this 15-year interval, the absolute necessity to create a number of research centers.

Now, these are not just groups of people. The centers at a maximum will be staffed by approximately 50 people working together.

To put that in perspective, there are many university laboratories now in existence which have 20 to 30 people working for a given scientist.

Our centers aren't ten times larger than groups pre-existing in most places. I think you could fit a research center in most universities and you wouldn't know they were there on the basis of their size.

We do have to have well-focused groups to get the project done economically. We don't want a $35 billion project.

If we didn't have the centers and we wanted to accomplish our goals, we would have to come to you and say the project is going to cost more.

We don't want that to happen. We want to really keep the costs down. We want to get these maps without putting an excessive drain on the budget.

COST OF RESEARCH CENTERS

Mr. NATCHER. Dr. Watson, your research centers cost more than some of the others in NIH generally. How do we justify it, Dr. Watson?

Dr. WATSON. Most of the centers at NIH are called core centers, where only shared facilities are provided. The centers themselves have a series of individual grants or program projects to investigators who use the facilities.

Our centers are specialized centers which are provided facilities and research funds. We initially considered supporting core centers and then providing separate additional funding for research, but we thought that would be inefficient.

To get the job done and be most efficient, we should fund the total cost of the project. The real cost to the program will be no more.

I think administratively it will be much more efficient. Otherwise, to support a research center, we might have to award five sparate grants.

The best way to look at it is by the number of individuals. It costs somewhere between $100,000 and $200,000, depending on the science being done, to actually support an active scientific function.

If we have a center which costs $4 million, we would think there are going to be between 30 and 40 people working in that center.

FUNDING PRIORITIES

Mr. NATCHER. Dr. Watson, assuming that we may be unable to appropriate the full amount that you request for 1991 do you consider it more important to preserve funding for research project grants or centers?

Dr. WATSON. You are asking me an almost impossible question. I think we need both. I think I can say that if we do not support research centers, we do not have a 15-year project.

CONSTRUCTION NEEDS

Mr. NATCHER. Last year there was talk of requesting language to create construction authority for your research centers.

Do you plan any construction for the centers?

If so, what authority will you use, Dr. Watson?

Dr. WATSON. Right now, we can only provide minor funds for renovation. In the center applications we have received, such funds have been requested in the first year's budget.

I think the project will go faster and the universities would be much more enthusiastic if we could help them with construction funds, but honestly, I think we can accomplish the project if the construction money isn't there. I would like it to be available if needed.

ORIGINAL REQUEST TO OMB

Mr. NATCHER. What was the department's original 1991 request for OMB for the national center?

Dr. WATSON. It was $133 million.

Mr. NATCHER. Okay.

Dr. WATSON. That did not include construction.

TIME SPENT AT THE CENTER

Mr. NATCHER. Dr. Watson, how much time are you able to spend here as far as the center is concerned?

Dr. WATSON. I am spending at least 2 days a week physically at the center. This week I will be spending 5 days.

When I am in my laboratory, I am frequently, if not the majority of the time, doing work for the center because the fax machine and the telephone are constantly going to keep me in communication with the staff at the center. I am talking with Dr. Jordan virtually every day.

I don't disappear and not think about the center. In fact, I can't think of anything more important to do.

My own institution, I think, is suffering, but they realize the importance of what I am doing here for the government.

Mr. NATCHER. Dr. Watson, do you expect to spend a greater portion of your time on the NIH campus over the next few years as far as the center is concerned?

Dr. WATSON. I have a competent staff surrounding me who can handle the day-to-day responsibilities of the center.

I don't feel that they are really unhappy when I am not there.

I think one has to say besides being in Washington D.C., it is very important for me to be in the places where the work is being done to get a feel for the job. I don't like flying that much, but I think it's necessary.

I was in Indianapolis 2 weeks ago explaining the Human Genome Project to respresentatives of the Eli Lily Company and then to those at Purdue University. I am spending quite a bit of my time talking about the project in different parts of the country.

I think that is a very important thing. I can't say that I am going to devote 100 percent of my time, but it is honestly moving toward 80 percent. Luckily again, the institution at Cold Spring Harbor is in very good shape. They are used to carrying on without me.

I do not have a crisis there which is going to take me away from Washington. I think my major job is to see that the Human Genome Initiative is successfully carried out.

INCREASES IN RESEARCH TRAINING

Mr. NATCHER. Dr. Watson, your 5 year plan sets the goal of supporting 600 research trainees by 1995. You request funds for 224 in 1991.

What sort of phase-up are you projecting, Doctor?

Dr. WATSON. We are gradually having a phase-up of about 75 trainees per year through 1995. It would reach approximately 524 in FY 1995 for NIH and the rest, approximately 76, would be supported by DOE.

NIH will be providing the vast majority of the training.

ADDITIONAL FULL-TIME EQUIVALENTS

Mr. NATCHER. Now, Dr. Watson, you are requesting eight additional full-time equivalents in 1991.

Do you envision further staff expansion in later years?

Dr. WATSON. Not significantly.

We hope we can build up the staff to accomplish the goals. This year we are making an addition to our staff in the bio-ethics area, to run the ethics program. We also want someone who will interact with American industry.

I was talking yesterday with my staff about trying to hire someone who would be concerned with education and training programs, and particularly seeing that we have a viable and meaningful program to bring minorities into our effort. We want to see it work.

I think if we don't hire an individual to do it, we will just say we are going to do it and it won't get done.

IMPORTANCE OF SEQUENCING

Mr. NATCHER. Dr. Watson, why is it important to complete the sequencing of the subunits of genes which number about 3 billion, rather than simply sequencing the 100,000 genes themselves?

Dr. WATSON. You can't really identify the genes until you do the sequence. You have got to identify the sequence because genes aren't at contiguous intervals separated by junk.

There is lots of so called "junk" within the genes which isn't really junk. It turns our to be quite a job to actually say this is your gene.

As a case in point, the gene for cystic fibrosis, isolated in Ann Arbor by Dr. Francis Collins, could have been isolated two years earlier, according to Dr. Collins, if he had the sequence available. That was a very, very fine piece of science.

The sequence is important, it is not just a luxury. In many cases it is going to be an absolute necessity. One of my chief objectives early on will be to try and sequence the region where we think a gene which predisposes to Alzheimer's disease is located. We want to see that sequence, we think it will give us a much better chance in finding the gene.

There has also been a great deal of difficulty getting the gene for Huntington's disease. Scientists know roughly where it is. It is at the tip of chromosome 4. It may be that we are going to have to sequence the DNA in the region. These sequencing projects are pretty big and really need to be supported by something like our research centers.

It involves building up a laboratory able to sequence 1 million base pairs. That is 10 times bigger than anyone has done in the United States with an ordinary grant. To focus on the immediate medical problems like Huntington's and Alzheimer's, we will need the sequencing capability.

YEARS OF RESEARCH TO USE GENOME INFORMATION

Mr. NATCHER. Dr. Watson, you estimate that sequencing the genome will take 15 years. After that, how many years of research will be needed to apply this information in the treatment of genetic diseases?

Dr. WATSON. I think we are always learning new things. There are always people who say we are going to know everything, and that has never proved to be true.

I think as long as human civilization goes on, we will be using that information to better understand ourselves and our diseases.

AVOIDING DUPLICATE EFFORTS

Mr. NATCHER. What are you doing to avoid duplication of effort among researchers who may be working on the same type of research?

Dr. WATSON. Right now at the level of our R-01, investigator-initiated, grants, we have some duplication. We don't quite know which is the best way to get the answer, so this is what I call healthy competition to pioneer new methods.

When we set up the research centers to complete the task, we are not going to set up two centers to do the same thing. The sort of fundamental unit which we will try to coordinate is the chromosome. So, there will be one place which will, say, look at chromosome 21.

These centers, I should make clear, will be where the data is kept and where much of the work is done. They are going to be coordinating their activities with large numbers of people outside the centers. In fact, the centers will be of great value to those individual people who have R-01 grants and are doing related research.

I think the centers should not be regarded as competitive, but a great help to all investigators. For example, we have a center application from San Francisco which includes a subcontract to Iowa. There is someone in Iowa working on the same part of that chromosome, so they will work together.

We are going to try to bring in many people so that they will feel part of a big team. We want to make everyone feel that they are both wanted and utilized. I think we will succeed.

DOE FUNDING REQUEST

Mr. NATCHER. Dr. Watson, how much funding is the Department of Energy requesting in 1991 for genome research?

Dr. WATSON. It is about $47.9 million.

JOINT REQUEST FOR APPLICATIONS

Mr. NATCHER. Have you ever thought about issuing a joint request for applications with the Department of Energy?

Dr. WATSON. We believe it is beter to coordinate our activities. We know which grant applications are received by both agencies. We think it would probably be healthy if you had two separate funds and two separate reviews, because we may make mistakes they may not and if they make a mistake, we may not. At this stage of the game, I think it is probably healthy.

The other thing is that the vast majority of the Department of Energy money will be spent within their national laboratories. Their program outside the DOE labs will be minor, whereas our program is really trying to go to the major medical centers, the major universities and the major companies within the United States.

FUNDING FROM OTHER COUNTRIES

Mr. NATCHER. How much funding are other countries contributing to the genome effort? Does any of this money support United States scientists?

Dr. WATSON. None of the money, to my knowledge, from foreign countries comes over here to support U.S. scientists. We have set up the rule that our money will be largely spent in the United States except when there are projects where there is joint collaboration between investigators from two countries. Then there might be an advantage for a relatively small amount of our money to be spent abroad to get the expertise we do not have in this country.

Major programs are being set up in France. In the United Kingdom there is also going to be a program, which I think, within 2 or 3 years will be sizeable.

The European Community program, I would say, is about 2 years behind us. I think it will be a sizeable program also.

In Japan, they have four different agencies supporting human genome research. It is not very well coordinated. The total sum of money is in the order of about $8 million a year. It is my hope that the Japanese will have a larger program and bear a considerable amount of the cost of the final sequencing.

HUMAN GENOME ORGANIZATION [HUGO]

Mr. NATCHER. Is HUGO, the human genome organization, an effective mechanism, Dr. Watson, to prevent duplication of effort in international research?

Dr. WATSON. Right now it is not because it really has been an organization in name only without any money. Over the past several months it looks like HUGO will receive money.

HUGO was having a meeting of their council in London yesterday and I think at least in Europe by, roughly, July 1, it will be a functional organization. I am counting on it.

There are big projects, particularly in the sharing of data, where we have to decide how the costs should be shared between the different countries.

Mr. NATCHER. Mr. Conte, I yield to you

Mr. CONTE. Thank you, Mr. Chairman.

Dr. Watson, it is truly an honor for us and the committee to welcome you here. Your work on DNA is the basis upon which modern genetics has grown.

Once again, you are on the cutting edge of bio-medical research with your leadership and genome initiatives. You ought to win another Nobel Prize for persistence.

Dr. WATSON. Well, let's wait for another 10 years.

USE OF RESEARCH CENTERS

Mr. CONTE. All right.

Dr. Watson, there has been considerable debate in the scientific community over your plans to base genome research from centers rather than investigator-initiated research grants.

Why do you think centers are the way to go in this type of research?

Dr. WATSON. In our FY 1991 budget, roughly half our money is going to go toward funding investigator-initiated research projects. We are not entirely a center program; research project grants will remain a very important aspect of our program.

The centers are necessary to get the cost of the project down to a reasonable level. When the genome program was first talked about, one could imagine spending $30 billion on it. That was unacceptable.

But to get the cost down to $3 billion, roughly $200 million a year, you have to create the centers which are going to say, for example, we will do the map of chromosome 7.

We are going to get the human genome completely mapped. If we don't have the centers, I don't think we will accomplish our goal in 15 years. It is just going to drag on and on, and we are going to have to wait longer to get this wonderful resource which the American medical community needs.

ROLE OF RESEARCH PROJECT GRANTS

Mr. CONTE. What role does R-01 research have in the genome project?

Dr. WATSON. It produces lots of exploratory ideas.

It produces many ideas which we can use in the research centers. Virtually every place where there could be a center already has research project grants.

Centers are also a way of coordinating. Some investigators who already have eight people on the program we think should go up to 25 and become a research center.

We promise people we are going to get these genetic maps in 5 years, so we want to get them in 5 years. If everyone is spending their time writing many different grant applications, we won't have efficiency.

We made the decision that we are not going to do this project by contracts. We are going to do it with grants.

We are not going to have someone looking over someone's shoulder. We are going to get people that we can trust and I think we are going to get the answer.

QUALITY CONTROL OF THE RESEARCH CENTERS

Mr. CONTE. What quality control mechanism will you have in place for these centers?

Dr. WATSON. Well, first in determining which grants to fund, there will be a very strong peer review by people in the field.

Mr. CONTE. Peer review?

Dr. WATSON. Peer review. It won't be the people at this table. We are just putting together that peer review group.

The second is we will be monitoring progress closely. We anticipate receiving applications from very good scientists.

No center will be funded where there are unqualified scientists. There are people who say this is bad science. That is not true.

This is very good science. The people who are going to receive funding will rank with the very best in the country.

STRUCTURE OF THE RESEARCH CENTERS

Mr. CONTE. How do you envision the centers are going to be structured?

Dr. WATSON. They will have to have one or two people who are scientific leaders. That is natural to have a good research group.

At MIT, where there are frequently 20 to 30 people in a group, there is usually a well-known professor who is in charge of each of the groups. The human genome research center, we hope, will have someone of international reputation as the leader. Sometimes they may be a little younger than some people might wish, but the younger they are, the better for me because they work hard.

Also, you know they are going to be around for 10 or 15 years.

Mr. CONTE. That isn't the case in all walks of life, though.

Dr. WATSON. No. I think I have gotten wiser with age. I am not sure I should be running 50 people and going in on Saturday mornings and Sunday nights.

INTERNATIONAL COORDINATION

Mr. CONTE. I understand other countries are interested in doing the human genome project and some currently have human genome mapping underway.

Who are the leaders in this abroad? How are you coordinating internationally?

Dr. WATSON. Two countries which I think are doing the best now are the U.K. and France. They are the ones that have the biggest program.

To coordinate them, we are organizing a series of meetings on specific chromosomes. In 2 weeks we are having a meeting here in Bethesda, MD on chromosome 21. We will have people from Japan, the U.K., and from France. So, we are constantly seeing the international people.

There will be a meeting at Cold Spring Harbor in late April where there will be about 300 people. Probably 100 of those will be from abroad. So, again we are constantly meeting with each other.

There will be a big meeting of gene mappers in London the first week in September. The mapping community of scientists are, on the whole, extremely friendly and cooperative. Where you get competition is when someone thinks they are going to isolate an important disease gene.

They want to do it ahead of someone else. That is the way science has always been done. There was a big race to get the cystic fibrosis gene.

People in London wanted it. Happily for us, Francis Collins and the people up in Toronto, discovered the gene. It was a sort of American-Canadian effort.

I am sure there will be an intense race to get the gene responsible for Alzheimer's, and that is good. However, when it gets down to spending tens of millions of dollars, we are not going to duplicate that sort of thing.

TECHNOLOGY DEVELOPMENT AND TRANSFER

Mr. CONTE. Are you working on ways to ensure that technology develops through this program and is developed commercially as effective as possible?

How will industry benefit from this project?

Dr. WATSON. We are appointing a person to our staff whose major concern will be seeing that the technology is developed and transferred to industry as rapidly as possible.

In order to get the cost down, in many cases we will be working with small instrument companies and so on. I think it is essential.

The second and equally important thing is when we get to the sequence data, it will be very interesting to people in industry. They are going to see every receptor for all these new re-transmitters. It is going to be exciting.

I was invited to go to Eli Lily to give a talk, and I spent about eight hours talking to the scientists about the Human Genome Initiative.

We want to organize a meeting next fall with the scientists from the major pharmaceutical companies within the United States to talk to them about how this data can best be utilized for the health of our own industry.

Last month I went to Florida to the Industrial Biotechnology Association and I talked to them about the project.

We want some work done in industry and then we want to be sure that this data doesn't go out in a way in which our industry doesn't get immediate benefit.

PCR TECHNOLOGY

Mr. CONTE. Throughout these hearings have you been impressed with the role of PCR reaction. What impact does PCR technology have upon the human genome project?

Will it contribute to lowering the cost of the project?

Dr. WATSON. Enormously. Inverse PCR will make the mapping much faster.

Three years ago people were trying for the maps and not doing very well. Now we know we can do it.

PCR was a great discovery. The inventor of it is a real example of a scientist. He did the work.

He succeeded. He didn't fail.

He has given the scientific world an immense tool.

You could say he reduced the cost of the project by 50 percent.

I hope he gets every scientific prize imaginable. He deserves it.

AVERAGE COST OF SEQUENCING

Mr. CONTE. Sure. What is the current average cost of sequencing a base pair. What efforts are underway to reduce the cost of sequencing?

Dr. WATSON. The average cost is still about $5 a base pair. You arrive at this by asking what does it cost to fund a scientist and then how many base pairs does he get out in a year?

If he has a graduate student working for him, it would cost us about $100,000 a year just to maintain the scientists, and he will

sequence about 20,000 base pairs per year. That is how the $5 is derived.

What is happening now is sequencing methods are moving from individuals doing it by the techniques worked out by Gilbert at Harvard and Sanger in Cambridge, England, around 1975, to doing it by machine.

There are currently machines produced by applied Biosystems and Dupont. There is going to be one produced by Pharmacia in Sweden, and the Japanese have developed a machine. Scientists are going to transfer the sequencing essentially to machines.

Over the past year it has moved from the situation where humans are still faster than machines to where machines are overtaking humans. The machines are going to be better than humans.

I think many of the steps are now being done by robots.

We have received five grant applications for demonstration projects which could at the end of 3 years prove they can do about 2 million base pairs a year and have the cost down to somewhat less than one dollar a base pair.

At NIH there is an investigator who organized a sequencing meeting at Wolf Trap. There, for the first time, we began to see the big data flowing out. I was very pleased. There will be a big sequencing meeting every year where the point will be just to keep the costs going down.

ETHICAL CONCERNS

Mr. CONTE. What are you doing about the ethical and social concerns that have been raised about the genome project?

Dr. WATSON. I think right now we want a lot of discussion. I am talking to every newspaper reporter who asks for an interview.

We are setting up a grants program which will encourage more confidence. We will try to encourage TV programs where we make people aware of what a genetic disease is and what the Human Genome Project means.

Eventually we are going to pass laws to assure people that when we get this genetic information, the only person who has the right to look at it is the individual person. No insurance company should have the right to look at my genes.

I think we would all be scared. I would be scared. But before we pass these laws, I think there ought to be a lot of discussion. It is complicated because some people don't even want to know.

The head of our Ethics Working Group's mother died of Huntington's Disease. As a result of this tragedy, she researched pedigrees in Venezuela which showed the gene to be located on chromosome 4. That was her response.

Now she could actually be tested to find out whether she is at risk but she doesn't want to know because she is 40 and has survived pretty well.

Maybe she will find she won't get the disease, but she doesn't want to know. Other people would say, "I want to know." I think that decision should be left to the individual.

I think that privacy is the issue. Certainly, I think a parent shouldn't have the right to test their child because eventually that child will grow up. These are the sort of social issues I would hope we will have identified and discussed.

Also in humans, we have genes that are called anti-oncogenes, whose absence predisposes to cancer. There has been extraordinary work done on them over the last couple of years.

We are going to be able to screen for some genes and say an individual is missing a copy of one of those. That might be very useful to tell someone who comes from a family where there is cancer.

Some people would want to be tested. You most certainly aren't going to smoke if you are missing one of those anti-oncogenes that protect from lung cancer.

I would say this is the type of data we are going to get. We can possibly say you are going to be predisposed to cancer. However, I wouldn't want an insurance company to look at the information.

This testing is identifying the risk. I think this is similar to the issue of the DNA fingerprint. The DNA fingerprint is an extraordinary tool in identifying criminals or proving innocence.

There is a national academy committee on DNA fingerprinting. I am sure the judges and lawyers on this committee will say whether they think there are going to be laws and what sort of laws there should be to prevent misuse of fingerprints.

I think the ethics committee is going to help set up these discussions which in some cases will lead to laws. We shouldn't rush into laws without a lot of discussion. There is not a crisis now.

Mr. CONTE. I agree with you.

Thank you, Mr. Chairman.

Mr. NATCHER. Mr. Obey, I yield to you.

ETHICAL CONCERNS

Mr. OBEY. Thank you, Mr. Chairman.

Dr. Watson, I am not going to take very long, but I would like to follow up on Mr. Conte's question.

Frankly, I have to confess to you, I think my attitude about the genome project is quite a bit different than it was when I first heard it. I was excited when I first heard it.

I was even more excited when you were given your responsibilities because there are very few people for whom I have more respect than you. But I wish I could be as sanguine as I think you are with respect to what we will do to, quote, "pass laws protecting human privacy."

I don't think that is the kind of era we are in. I think we are in an era where large institutions in this society determine what is going to happen, and the individual most often gets crunched.

I see a drive toward, for instance, for mandatory drug testing by employers. I think it is a very short leap from mandatory drug testing to other kinds of testing that employers might ask for when you get wrapped into liability questions.

I am very concerned about the potential for this kind of research destroying principles such as group insurance. I guess I am wondering whether or not we are not in danger of proceeding too fast with this.

I guess my concern is this. Of the amount you are going to be spending this year, how much is—you mentioned Nancy Wexler. She indicated the Federal Government was prepared to set aside 3

percent of the funding to examine the ethical issues associated with these questions?

Dr. WATSON. Yes.

Mr. OBEY. Do you think that is sufficient—do you really think we ought to be pursuing this as fast as we are before we have—I mean if I thought we were going to pass the kind of laws you are talking about, I would feel a lot more comfortable. But, my instincts tell me we are not.

Dr. WATSON. I don't think we ever do anything until we have a crisis. I don't think before we get the data society will think about it.

Our ethics program will prepare us for the data. But, if we didn't get the data, we wouldn't be able to discuss the ethics.

It would be as if it were not real. Society has so many crises that it is hard to respond to a non-crisis.

Mr. OBEY. You know, I guess my problem with that response is that I think that the more people know we know, the more the large institutions in this society are going to insist that they can use that knowledge in the most efficient way possible.

I think that the drive for human efficiency is very much at odds with a rational resolution of these issues. What can you point to besides your personal hope?

What can you point to to demonstrate that we are developing a conscience to pass the kind of laws that you are talking about?

Dr. WATSON. Well, may I put the dilemma in this way? I think quite probably our only way of combatting Alzheimer's disease is to locate the gene and just find out what initiates the process.

Now, should we not find the gene because we are worried if we find the gene someone will use it to do random testing. We already have an enormous problem which is growing with Alzheimer's. We also have enormous problems with mental disease.

Again I think finding the genes is probably our only way of fighting the disease. That is just my scientific feeling.

ETHICAL CONCERNS

Mr. OBEY. I am not suggesting we shouldn't find the genes. I guess I am asking shouldn't we insist that there be certain understandings about the way this knowledge is going to be used before we proceed to develop it?

Dr. WATSON. I am afraid, given society, we won't get an understanding. I can't imagine a law being passed before the data is available. I think we will see laws in the case of the DNA fingerprint.

I have heard people say we should have a national register. Well, in certain hands that data could be used wrongly. I wouldn't want the local police chief of the village to be able to look at the DNA fingerprints of everyone in the village.

I think the question will we get laws to prevent misuse is open, because we currently have a technique which is very important for criminal justice. I don't think we should not have developed DNA fingerprints until after a law was passed to protect usage of the data.

COMPETING FISCAL REQUIREMENTS

Mr. OBEY. I am not suggesting that we shouldn't proceed with research. What I am wondering is what you are talking about is the speed with which we pursue the knowledge.

I guess, you know, standing alone I think the issue is worth considering. But, I also happen to think that we are in an era in which we are not going to see very much by way of expansion of budgets for the kind of research that this committee supervises. I think that is the kind of era we are in.

And I think the way our science budget is likely to be sliced up over the next few years, I think you are going to see a lot going into the space station, a lot going to the super collider and much less going into a lot of other science projects.

I guess concurrent with my concern about the lack of ethical determinations is also my concern that we are not seeing the kind of expansion in support for R-01's that I would like to see.

I am wondering whether we would really be doing any great long-term damage if we were to go to $100 million of money to expand R-01's.

Dr. WATSON. I think our project is most important to the mission of the National Institutes of Health which is becoming genetics dominated more and more.

Mr. OBEY. Let's grant that it is more important long term. Does that mean that we would be making a mistake if over the next two or three years we slowed you down to expand R-01's until we had a little bit of footing on the other question?

Dr. WATSON. Because I think what we are doing is more important. That is not saying I do not appreciate the need for investigator-initiated research project grants. I would make a very strong argument that we need more money for R-01 as well as our program.

Mr. OBEY. With all due respect, that is begging the question. Mr. Conte and I just came from a meeting at the White House.

We were told in no uncertain terms there that the money that we ought to spend in supplementals should be for Panama, for Nicaragua and to hell with domestic programs. That is the marching orders we were given by at least some people.

Dr. WATSON. I never thought you took marching orders.

COMPETING FISCAL REQUIREMENTS

Mr. OBEY. Well, I guess I would simply observe that much as we would both like to see expanded medical research, I don't think that will happen.

If you thought that the real dollar value going into R-01's for the next 5 years would remain constant, would you still feel we ought to continue to devote the $200 million?

Dr. WATSON. Yes, because I think a lot of the R-01 objectives have no chance to succeed without finding the genes.

I have seen this with cancer research. I know why we have succeeded and I know why we are not succeeding in some of these other cases. We have a very tough objective. I frequently get letters from people with children, you know, families, parents, with mental disease.

They are just crying out for someone to have the guts to go after their problem. I have the guts to go after it.

Mr. OBEY. I guess all I can say is I respect your opinion greatly. I am still not fully convinced, frankly.

I guess all I would urge you to do is to, what I would like to see next year when you come before this committee, I would like to see some indication that there is a strategy in association with the development of your project. That there is a strategy to bring this society to some conclusions about some of the ethical questions involved.

I honestly think that though we might have high hopes now about the kind of protections that society would afford this morning, I think that the more we learn about it, the less likely we are to have the troops in the political field to guarantee the protection of that knowledge that I think you think is essential.

I don't know what the amount is. I don't know if it is important that you spend 3 percent or 2 percent or 5 percent on these questions.

I don't think it is so much the amount as the determinations to focus on that area. I think you should not underestimate the weakness of the political system in terms of its ability to deliver the kind of protections that need to be afforded that information.

I think regrettably that the political system is very, very weak there.

Dr. WATSON. I think you raise very difficult issues. Maybe I am more optimistic than I should be.

Mr. OBEY. You know what is said about an optimist. An optimist is a guy who ain't had much experience.

You have had a lot of experience and so have I.

Dr. WATSON. I am still an optimist.

Mr. OBEY. Perhaps you see more improvement in your field than I have in mine, which is why we have differences about those judgments.

Dr. WATSON. I heard an interesting comment which was related to people who have manic depressive disease, that people always have to be more optimistic than they should be.

You never take into account the new things which are going to happen, at least in science. A lot of people think I am sightly crazy to pursue this project.

But I don't think history will show that I was wrong. I don't want to just see alcoholics, I want to find the gene which may be responsible for the disease. I had a meeting of scientists who are fighting for that.

It is the sort of thing we can go after with a program like this. We have very big objectives. You could say why not wait for a few years?

I always thought there was a sort of rush in life to get something done. The rest of the people will say "he is just a visionary". But if you don't support visions, it would be like living in Russia.

ETHICAL CONCERNS

Mr. OBEY. I am very interested in pursuing visions, but there are dark visions as well as bright ones. I guess all I would say is that

our Founding Fathers recognized, they designed a system to take into account that they were not optimistic about human nature.

In fact, they were very skeptical about it. That is why they build all kinds of checks and balances and protections.

I don't think society has a good track record in protecting privacy. I think it has a lousy record.

I think when you are talking about developing a strategy to protecting as basic and as private as the information that you are developing, I think we have got to be skeptics in terms of—if we are not skeptics, we are not going to take into account sufficiently, in my view, the protections that have to be built in in order to protect the individual.

I really would urge you to—I would feel a whole lot more comfortable if you could come before us next year and show me that in addition to your hope, there is in your operation some strategy in mind to try to force decisions along in this other area as you are forcing knowledge along in the primary area.

Dr. WATSON. We will be very pleased to do that. I think that is a very excellent request.

I do say that I don't think you are going to get meaningful discussion from people about these issues unless you are accumulating the data. I don't think you can get people to talk about the ethics until the need arises

Mr. OBEY. I grant that. That is why I am not suggesting that we shut down the project. I am simply expressing misgivings about it.

Thank you.

Mr. CONTE. I have some questions.

Mr. NATCHER. Go ahead.

ACCESS TO HUMAN GENOME DATA

Mr. CONTE. I have many questions I will put in the record.

I was interested, Dr. Watson, there were reports which implied you threatened to withhold genome data from the Japanese unless they contributed funds to the project in the human genome organization. Comment on these reports.

What is your access to records on the genome data?

Dr. WATSON. My aim is to get as much cost sharing as possible so all the countries in the world would help. Then it will be very easy to exchange the data. I think the data will eventually be released, but I think cost sharing will determine the speed at which the data will be released.

If persons pay for the project, they should have the right to examine the data and get everything out before I pass it on. That is just my idea. I think this idea will make other countries want to put some money into the project.

I think it will be exciting science. But I can't see the French letting us have the data without collaboration..

Mr. CONTE. They are not?

Dr. WATSON. Not unless we work together.

Mr. CONTE. Thank you.

Mr. NATCHER. Dr. Watson, we want to thank you and your associates for appearing before our committee in behalf of your budget request for fiscal year 1991. It has been a good hearing, Doctor.

Thank you very much.

[The following questions were submitted to be answered for the record:]

INTRAMURAL RESEARCH PROPOSALS

Mr. Natcher. You are allowing in-house researchers from other Institutes to apply for your research project grants. Is this a common practice throughout NIH?

Dr. Watson. The NCHGR is currently concluding the first round of review of genome-related proposals from intramural investigators. We were very encouraged by the interest shown by the intramural community in this program and we anticipate that we will be able to announce some awards soon. The intramural applications were reviewed by a peer review committee similar to those used to review extramural applications. The funds to support the successful projects will be taken from the contract line of the NCHGR budget and administered as intra-agency agreements, thus the awards are not research project grants. Although the Office of the Director, NIH, held a similar competition for intramural AIDS researchers, the details of the review and award of the AIDS projects differ from those of NCHGR. We believe that the NCHGR model is unique for the intramural program and has provided a useful way to include intramural researchers in the genome project.

CONTINUATION OF THE NATIONAL CENTER FOR HUMAN GENOME RESEARCH

Mr. Natcher. Would you expect the National Center to go out of existence once the genome project is completed?

Dr. Watson. Very likely, yes. The mapping and sequencing of human chromosomes will never be entirely finished, because once we have completed one genome we will want to study variations between individuals, but the rationale for the existence of a separate organization to coordinate work in this area may evaporate once there are relatively complete genetic linkage maps, physical maps, and reference DNA sequences.

FUNDING FOR HUMAN GENOME INITIATIVE

Mr. Natcher. Provide a chart listing Federal funding for genome mapping by Department and funding provided by foreign countries for 1988-90.

Dr. Watson. The information follows:

UNITED STATES FUNDING FOR HUMAN GENOME PROJECT
(Dollars in millions)

	FY 1988 Actual	FY 1989 Actual	FY 1990 Estimate
Nat'l Ctr for HG Research	17.2	28.2	59.5
Department of Energy*	10.7	18.5	27.9
Total U.S. Funding	27.9	46.7	87.4

*Excludes salaries and expenses of DOE employees devoted to this effort

INTERNATIONAL FUNDING FOR HUMAN GENOME INITIATIVE
(Dollars in millions)

	FY 1988 Actual	FY 1989 Actual	FY 1990 Estimate
United States	27.9	46.7	87.4
Italy	1.5	1.4	2.0
United Kingdom		5.9	5.9
Union of Soviet Socialist Republics		2.0	2.0
Japan		4.3	6.3
Comm. of the European Community	4.0	13.0	13.0
UNESCO		*	.1
Total Funding**	33.4	73.3	116.7

* Funding less than $100,000
** Funding for other countries has been converted to dollars and is prorated proportionally, since projects are not funded on a yearly cycle.

A FIVE-YEAR PLAN FOR THE HUMAN GENOME PROJECT

Mr. Natcher. Insert in the record at this point the five-year plan for the genome project requested by the Committee in its 1990 request.

Dr. Watson. The following is the Executive Summary of A Five-Year Plan for the Human Genome Project. The complete text is available from the National Center for Human Genome Research at (301) 402-0911.

A FIVE-YEAR PLAN FOR THE HUMAN GENOME PROJECT

EXECUTIVE SUMMARY

In House Report No. 101-172, the Committee on Appropriations requested that a comprehensive spending plan be developed for the National Center for Human Genome Research prior to hearings on the 1991 budget (page 84). The following is submitted in response to that request.

The Human Genome Initiative is a worldwide research effort that has the goal of analyzing the structure of human DNA and determining the location of the estimated 100,000 human genes. In parallel with this effort the DNA of a set of model organisms will be studied to provide the comparative information necessary for understanding the functioning of the human genome. The information generated by the human genome project is expected to be the source book for biomedical science in the 21st century and will be of immense benefit to the field of medicine. It will help us to understand and eventually treat many of the more than 4,000 genetic diseases that afflict mankind, as well as the many multifactorial diseases in which genetic predisposition plays an important role.

A centrally coordinated project focussed on specific objectives is believed to be the most efficient and least expensive way of

obtaining this information. In the course of the project much new technology will be developed that will facilitate biomedical and a broad range of biological research, bring down the cost of many experiments, and find application in numerous other fields. The basic data produced will be collected in electronic databases that will make the information readily accessible in convenient form to all who need it.

This report describes the plans for the U.S. human genome project and updates those originally prepared by the Office of Technology Assessment (OTA) and the National Research Council (NRC) in 1988. In the intervening 2 years, improvements in technology for almost every aspect of genomics research have taken place. As a result, more specific goals can now be set for the first 5 years.

The plan presented here was prepared jointly by the National Institutes of Health (NIH) and the Department of Energy (DOE), the two agencies that have received earmarked funding for the human genome project. Over the last 2 years, these agencies have developed a highly synergistic and well-integrated approach to carrying out this initiative, as evidenced by the adoption of this common plan.

In order to achieve the scientific goals set out in this report, a number of administrative measures have been put in place. In addition a newsletter, an electronic bulletin board and a comprehensive administrative database are being set up to facilitate communication and tracking of progress.

Research centers will be established to promote the collaboration of investigators from diverse disciplines on a major task of the genome program. DOE has already established 3 large centers in its national laboratories and NIH will establish 10 to 20 additional centers over the next 5 years. The centers will become foci for collaboration with investigators at other locations and with industrial organizations that want to develop applications of the research results, thereby creating networks of interrelated projects.

Meetings and workshops will be organized to bring together investigators with common research objectives and to encourage collaboration, exchange of materials and use of common starting materials or protocols wherever these are appropriate. It is expected that mapping and sequencing groups will coalesce around individual human chromosomes or around particular model organisms.

NIH and DOE will continue their synergistic working relationship and will also interact closely with other interested agencies as well as with genome mapping programs in other countries as these get organized. Close ties with industry and with the medical community have been established, and will continue to be encouraged, to ensure efficient technology transfer. The private sector is involved in this project at all levels from participation in the advisory committees to receipt of grants and contracts.

The overall budget needs for the effort are still anticipated to be the same as those identified by the OTA and the NRC, namely about $200 million per year for approximately 15 years. Fiscal years 1988 to 1990 have been a period for getting organized and getting research

under way. The 5-year goals that have been specified in this plan are for the period FY 1991 through FY 1995 and assume the program will rapidly reach the level of funding specified above.

SCIENTIFIC GOALS

In addition to the long-term objectives of the human genome project, this plan sets out specific scientific goals to be achieved in the first 5 years together with the rationale for each goal. Five-year goal have been identified for the following areas, which together encompass the human genome project:

* Mapping and Sequencing the Human Genome

* Mapping and Sequencing the Genomes of Model Organisms

* Data Collection and Distribution

* Ethical and Legal Considerations

* Research Training

* Technology Development

* Technology Transfer

The specific goals will be reviewed annually and updated as further advances in the underlying technology occur.

FIVE-YEAR ESTIMATES FOR THE HUMAN GENOME PROJECT

Mr. Natcher. Provide the five-year cost estimates that were prepared but not included in the five-year plan.

Dr. Watson. We have prepared a preliminary mechanism break for fiscal years 1991 through 1995 representing our best professional judgment of what will be needed in this time period. This table is based on $200 million per year for the U.S. program, without taking into account the effects of future year inflation, and assuming two-thirds of this amount is allocated to NIH and one-third to DOE. I would like to note that it is difficult to fix a particular budget distribution at this time in such a rapidly moving field, where relative costs and technology is changing constantly. Flexibility will be essential so that unexpected opportunities can be pursued effectively. Every effort will be made to complete the project as economically as possible.

Finally, these estimates reflect our professional judgment and have not been reviewed by the Administration in comparison with other scientific priorities.

National Center for Human Genome Research
Fundings Estimates for FY 1991 through FY 1995
(Dollars in millions)

	FY 1991 Pres. Budget		FY 1992 Estimate		FY 1993 Estimate		FY 1994 Estimate		FY 1995 Estimate	
Research Grants	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Proj.:										
Noncompeting	117	34.9	151	49.1	127	41.3	114	37.9	106	35.2
Competing	53	17.7	53	17.7	53	17.7	48	16.0	43	14.3
Subtot.,RPGs	170	52.6	204	66.8	180	59.0	162	53.9	149	49.5
Research Centers:										
Spec/comp.	9	35.7	11	43.7	12	47.6	13	51.6	14	55.6
Subtot.,Centers	9	35.7	11	43.7	12	47.6	13	51.6	14	55.6
Other Res.:										
Careers	12	0.9	15	1.0	15	1.1	15	1.1	15	1.1
Other	18	1.8	20	2.0	20	2.0	20	2.0	20	2.0
Subtot.,Other	30	2.6	35	3.0	35	3.1	35	3.1	35	3.1
Total, Res Grants	209	90.9	250	113.5	227	109.7	210	108.6	198	108.2
Training	FTTP									
Individual	75	1.9	100	2.6	150	3.9	175	4.5	175	4.5
Institutional	149	3.2	199	4.2	319	6.7	341	7.2	349	7.4
Total, Training	224	5.1	299	6.8	469	10.6	516	11.7	524	11.9
R&D Contracts	5	8.0		8.0		8.0		8.0		8.2
RM&S		4.0		4.7		4.7		4.7		4.7
Total, NCHGR		108.0		133.0		133.0		133.0		133.0

Note: Table was prepared without taking into account the effects of future year inflation

NIH AND DOE COORDINATION

Mr. Natcher. Would you insert in the record at this point a short history of the Department of Energy's involvement in the human genome project. Also include a statement describing the current division of labor between NIH and Energy and also tell us the rationale for the two-thirds/one-third split of the proposed $200 million budget for this project.

Dr. Watson. The genome program of the Department of Energy started in FY 1987 on a small scale and received earmarked funds for the first time in the FY 1988 appropriation. DOE's genome activities are represented mainly by multidisciplinary programs under way at three National Laboratories: Lawrence Berkeley Laboratory; Los Alamos National Laboratory; and Lawrence Livermore National Laboratory. Additional projects are supported at other national laboratories, at universities and in the private sector.

Oversight of DOE human genome activities is provided by the Health and Environmental Research Advisory Committee (HERAC). The Office of Health and Environmental Research (OHER), assisted by the DOE Human Genome Steering Committee representing the three national laboratories and extramural grantees, manages the program and administers grants and contracts.

Although the National Institutes of Health and the Department of Energy are equally interested in attaining the knowledge that will flow from mapping and sequencing the human genome, the two agencies are working to carry out the project in ways that take advantage of each organization's particular strengths and at the same time complement the genome program of the other agency.

The National Institutes of Health has a keen interest in the Human Genome Project that stems from its long history of supporting research in genetics and molecular biology as an integral part of its mission to improve the nation's health. NIH brings to the project a particular interest and strength in human genetics and biology as well as a commitment to studying model organisms along with the human genome.

The Department of Energy has a long-standing program of genetic research for assessing the effects of radiation and energy-related chemicals on human health. DOE strength is in technology development and computer science.

The funding split between the NIH and DOE is approximately two-thirds/one-third in FY 1990 and the ratio in the FY 1991 request in about the same. It is assumed that this distribution will remain. However, the actual distribution will depend on decisions made by the President and the Congress.

CONSTRUCTION FUNDING

Mr. Conte. Will funding for construction be needed to establish the genome research centers?

Dr. Watson. We expect to provide renovation funds for setting up the centers initially. However, as the projects expand, additional space would be helpful to house the growing center.

Mr. Conte. What would happen if construction funds are not available?

Dr. Watson. If construction monies are not available, the growth, and therefore scientific progress in the centers may be slowed and the completion of the project may be delayed.

COLLABORATION THROUGHOUT NIH

Mr. Conte. Your project has important collaborations throughout NIH. How will you coordinate your efforts with the other institutes at NIH?

Dr. Watson. At the NIH we have a trans-NIH coordinating committee for this purpose. We provide information regularly to the other Institutes, my staff has visited a number of the Institutes and their Advisory Councils and conversely they have sent representatives to our Advisory Committee meetings. In organizing conferences we generally include individuals who are likely to use the data and technology produced by the genome project and are grantees of other Institutes.

We have recently begun an NIH-wide, NCHGR sponsored seminar series as another means of informing the NIH community of our activities. Leading NCHGR investigators will be asked to present their work at these seminars. We will also ask the intramural investigators who have received NCHGR funding to participate in the seminar series.

Mr. Conte. For the record, please summarize your collaborative efforts with each NIH institute and your projected plans for the coming year.

Dr. Watson. A recent example of our continuing collaborations with other NIH Institutes was the meeting held in March 1990 to discuss the technical aspects of widespread cystic fibrosis (CF) testing. This meeting was jointly sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NCHGR and several other institutes. While the CF work and the issues surrounding genetic testing for CF are the direct responsibility of the NIDDK, NCHGR will need to consider the same issues as our investigators map and sequence DNA regions containing disease genes. As another example, NCHGR and the National Institute of Child Health and Human Development (NICHD) are jointly supporting a meeting scheduled for April, to discuss the physical mapping of human chromosome 21.

The NCHGR has an ongoing relationship with the staff of the National Institute of General Medical Sciences (NIGMS). Much of the research and training supported by the two organizations is closely related. Therefore we regularly negotiate with NIGMS for secondary assignments on their research and training grant applications. We currently co-fund a National Cancer Institute (NCI) research grant and expect that we will be able to use this mechanism in the future to promote genome-related studies within more mission-oriented laboratories. We have held discussions with the staffs of the National Institute on Aging (NIA), the National Center for Nursing Research (NCNR) and the National Center for Biotechnology Information (NCBI) of the National Library of Medicine (NLM) to review the goals of our programs and theirs and to discuss areas of common interest.

The NCHGR is actively collaborating with the NCBI. Many of the projects that the NCBI is undertaking will support genome-related efforts. For example, it is planned for the NCBI to assume the administration of GenBank, a genomic database, in the next three years. The maintenance of GenBank will be extremely important to the Human Genome Project since it may serve as the repository, or at least as a prototype repository, for the genome sequence data. Staff from NCHGR is working closely with the NCBI in designing the next generation of GenBank. In addition, NCHGR and NCBI have jointly funded genome activities such as the Human Gene Mapping Workshop held last summer.

An important element in the Human Genome Project will be the transfer of newly developed technology to the private sector. In order to promote such transfer, the NCHGR has held discussions with the NIH Office of Technology Transfer (OTT). In addition to hiring an individual for NCHGR to promote this activity, the NCHGR expects to continue to work closely with the OTT in this critical area.

The NCHGR is formulating an aggressive plan to include minorities in the Human Genome Project. A part of this plan is to work closely with the Research Centers in Minority Institutions (RCMI) Program of the National Center for Research Resources, to develop foci of genome-related research in minority institutions. We have met with Dr. Sidney McNairy, Program Director for the RCMI program, and expect to jointly support a meeting to discuss opportunities in the Human Genome Project with minority investigators.

POTENTIAL USES OF THE GENOME PROJECT INFORMATION

Mr. Conte. What are the potential uses of the genome project for clinical medicine in the coming decade?

Dr. Watson. The principal benefits will be tools to better understand genetic diseases and the genetic factors that underlie other diseases such as heart disease and mental illness. The main purpose of the genome project is to make everyone else's research easier, faster, and cheaper.

In addition, however, there will be direct clinical spinoffs from the technical innovations in genome research. These would include diagnostic tests for infections, cancer, and genetic diseases. Any test that involves the direct analysis of DNA can potentially benefit

from advances in genome research. The resulting information from gene maps and sequencing will also expedite direct genetic approaches to disease, such as somatic cell gene therapy--insertion of new genes to treat a patient in a way that does not lead to inherited changes.

Beyond the next decade, the genetic understanding of disease will transform our thinking about disease, just as biochemistry did in the 1960's and bacteriology did early in this century.

RESEARCH TRAINING

Mr. Conte. With the rapid growth of the center, what do you foresee as the research training needs in the coming year and the next five years?

Dr. Watson. Some of the important problems that need to be overcome in order to meet the goals of the Human Genome Project will require interdisciplinary solutions, applying the approaches of the biological sciences in conjunction with those of sciences such as physics, mathematics, computer science, chemistry, and engineering. However, it is widely perceived that there is a shortage of scientists who possess the necessary constellation of skills to engage in such multidisciplinary approaches. Therefore, the NCHGR plans to encourage and support institutional and individual training programs that emphasize interdisciplinary education in one or more of these other sciences and areas of biomedical research relevant to genomic analysis. The programs being developed will train independent investigators in the skills necessary for them to participate in the mapping and sequencing endeavor and, furthermore, allow them to analyze and use genomic information in their future research.

To meet these needs, the 5-year plan for the Human Genome Project set a goal of increasing the number of trainees supported by the program to 600 per year--aggregate total for NIH and DOE--by the fifth year. To meet this goal, the NCHGR has requested funds to support 224 trainees in FY 1991--75 post-doctoral fellows and 149 pre-doctoral trainees. By FY 1995, the NCHGR hopes to support 524 trainees--175 post-doctoral and 349 pre-doctoral--as its share of the total number of trainees.

A FIVE-YEAR PLAN FOR THE HUMAN GENOME PROJECT

Mr. Conte. Last August a group of NIH and Department of Energy advisors met to develop a joint plan for the project for the next five years. What is the status of the five-year plan?

Dr. Watson. The five-year plan for the Human Genome Project was approved by the NIH Program Advisory Committee on the Human Genome in December 1988 and the DOE Health and Environmental Research Advisory Committee in January 1989. Recommendations from both advisory committees were incorporated into the plan, and the plan was then put into the clearance processes of both the Department of Energy and the Department of Health and Human Services. Once final approval is received from both departments, the five-year plan will be printed

and widely distributed to the scientific research community, Congress, the media, professional associations, other executive branch agencies, and the lay public.

Mr. Conte. What are the key recommendations so far?

Dr. Watson. The key recommendations are specific scientific five-year goals that have been established and endorsed by the genome advisory committees of both the Department of Energy and the National Institutes of Health. Five-year goals have been identified for the following areas, which together encompass the Human Genome Project:

o Mapping and Sequencing the Human Genome

o Mapping and Sequencing the Genomes of Model Organisms

o Data Collection and Distribution

o Ethical, Legal, and Social Considerations

o Research Training

o Technology Development

o Technology Transfer

These five-year goals will be reviewed annually and updated as further advances in the underlying technology occur.

Mr. Conte. What are the major responsibilities of each Department during the duration of the project?

Dr. Watson. The major responsibilities of NIH's National Center for Human Genome Research and DOE's Human Genome Program will be complementary, but there are also clear areas of distinction based on each agency's interests and strengths.

Medical applications of genomic research will be a particular strength of the NIH human genome program. The National Center for Human Genome Research plans to devote considerable effort to completion of the human genetic map, which will be a valuable tool for scientists working to identify and eventually isolate disease genes. The NIH genome program includes the study of the genomes of model organisms, which will ultimately contribute to technology development and to the interpretation of the human DNA sequence. Funding public databases, which will be the repositories for information generated by the project, is also a major responsibility of the NIH. The NCHGR will support a comprehensive training program for pre-doctoral, post-doctoral, and senior investigators, as well as a career development program. These programs are aimed at addressing the current and future needs of genomics research.

The Department of Energy is emphasizing the development of the computational tools needed to enter, retrieve, and analyze mapping and sequencing data in large databases. The program also will focus on the innovation of new concepts and technologies for mapping and sequencing that will assist in the rapid, cost-effective analysis of

DNA. The DOE will provide support for pre-doctoral and post-doctoral individuals training at the National Laboratories to increase the pool of future researchers.

Both NIH and DOE are interested in the physical map of the human genome, as well as in the development of sequencing technology. These are very large and challenging goals that will require a concerted effort by both agencies. Since the methods for achieving these goals are continually being improved and rapidly changing, parallel approaches are necessary and desirable. The NIH and DOE also will share responsibility for dealing with the ethical, legal, and social implications of the genome project. A Joint Working Group on Ethical, Legal, and Social Issues was created to anticipate concerns before they arise, and develop policy options to address such concerns. The Joint Informatics Task Force and the Joint Mapping Working Group also were established to foster cooperation and collaboration between the two agencies during the course of the genome project.

Mr. Conte. How is each department's role different?

Dr. Watson. Although the National Institutes of Health and the Department of Energy are equally interested in attaining the knowledge that will flow from mapping and sequencing the human genome, the two agencies are working to carry out the project in ways that take advantage of each organization's particular strengths and at the same time complement the genome program of the other agency.

The National Institutes of Health has a keen interest in the Human Genome Project that stems from its long history of supporting research in genetics and molecular biology as an integral part of its mission to improve the nation's health. Most of the research supported by the National Center for Human Genome Research will take place at academic, non-profit, or for-profit institutions across the country.

The Department of Energy has a long-standing program of genetic research for assessing the effects of radiation and energy-related chemicals on human health. DOE's Human Genome Program will conduct genome research primarily through activities being carried out at three of their National Laboratories: Lawrence Berkeley Laboratory; Los Alamos National Laboratory; and, Lawrence Livermore National Laboratory.

JOINT INFORMATICS TASK FORCE

Mr. Conte. What is the mission of the Joint Informatics Task Force?

Dr. Watson. The mission of the Joint Informatics Task Force (JITF) is to identify the needs of users of genome information, to set genome informatics goals, to establish priorities and to make recommendations to the NIH and DOE Human Genome Committees in both technical and policy areas relating to: genome database structures, management and services; informatics tool development, data interchange standards, networks supporting electronic access to

genome information, informatics research training and education, and interagency and international informatics coordination and cooperation.

GENOME INFORMATICS

Mr. Conte. What is genome informatics?

Dr. Watson. The term informatics refers to computer-based activities that are required to store, analyze and distribute data. The data in the genome program are the data items that describe physical maps, genetic maps, DNA sequence and accompanying data that add detail to the basic information. Informatics activities in the genome project include the development of local laboratory based, as well as public, databases to store information and to provide access to the stored data. Software is needed to use and analyze the data. Computer networks, as well as tapes, diskettes and CD-ROMS, are used to distribute the information from the laboratories that produce the data to the public repositories and then out to the community. Although informatics researchers have developed tools to support data collection, analysis and distribution, we expect that much more sophisticated systems will be needed for handling the large and complex amount of data to be generated by the genome project.

MINORITY RECRUITMENT

Mr. Stokes. You currently have 30 FTE's in the Center and you are requesting 8 more. Have you been able to recruit minorities? I am particularly interested in positions GS/GM 13 and above.

Dr. Watson. The staff of the National Center for Human Genome Research is quite small. Currently, only 25 positions have been filled. We have made a considerable effort to hire minorities. Forty percent of the staff are minorities. Eleven staff members are in positions GS/GM 13 and above and of the eleven, two are minorities.

COLLABORATION WITH THE RCMI PROGRAM

Mr. Stokes. We discussed briefly with Dr. Whitney yesterday the initiative that you are undertaking with the RCMI institutions. Can you tell me what future plans you have to further involve these schools in human genome research?

Dr. Watson. We plan to jointly sponsor a meeting with the RCMI program this summer. One of the expected outcomes of the meeting will be to get an indication of the specific research interests and capabilities of the RCMI institutions in genomic research. Using this information, we will work with individual institutions and investigators to develop plans which will meet their specific needs and may include training opportunities through the National Research Service Awards, curriculum development, support to attend scientific meetings on the human genome, enhancement of research efforts through the minority supplements or investigator initiated research awards, as well as funding to improve the infrastructure for genomics research.

MAPPING OF MODEL ORGANISMS

Mr. Stokes. How useful is mapping and sequencing the DNA of organisms such as bacteria, yeast, and fruit flies? What can be learned from this? And how much is currently being spent on these model organisms?

Dr. Watson. Experience in biomedical research has shown many times over that information derived from studies of the biology of model organisms is essential to interpreting data obtained in studies of humans and in understanding human biology. Research involving microbial and animal models will continue to provide a basis for analyzing genetic diseases, normal gene regulation, and evolutionary processes. For example, yeast share with animal cells many of the molecules and processes that are being studied in modern cell biology, including factors that modulate cell structure and dynamics, components of the machinery that modulate protein secretion from cells, constituents of basic chemical pathways, and analogs of several mammalian oncogenes.

Model organisms are also essential to technology development. Since the genomes of model organisms are smaller and simpler than

that of human and can be manipulated more easily, they represent excellent systems for developing and testing procedures which will eventually be applied to the complex human genome.

In FY 1989, the NCHGR supported 103 grants at a level of approximately $28 million; approximately $11.5 million went to support research on model organisms.

RESEARCH TRAINING

Mr. Stokes. Your budget request would significantly increase research training, from 135 to 224 trainees. What can you tell us about the manpower needs for this field? Is the research program getting ahead of the supply of trained researchers?

Dr. Watson. For a new field, there is always the danger of the research program getting ahead of the supply of trained researchers. The number of scientists who presently identify themselves as working in genomic analysis, is understandably limited. However, genomic analysis is closely related to the areas of genetics and basic molecular biology that have been supported by NIH for many years and it is not surprising that an increasing number of scientists are being attracted into the area. One good indication of this movement is the increasing number of research grant applications being received from scientists who have chosen to redirect their efforts in genome-related activities. The training programs being developed are designed to encourage and support this trend.

Mr. Stokes. Will you make a special effort to train minority researchers?

Dr. Watson. The NCHGR realizes the importance of training minority scientists to participate in the human genome program, not only to help the NCHGR achieve its current goal of mapping and sequencing the human genome, but also to apply this information in understanding human pathology and in developing effective therapies once the goal has been accomplished. We are committed to finding creative ways to achieve this goal. Institutional training programs will be expected to recruit and retain minority students. Minority faculty will be encouraged to apply under the senior National Research Service Award program to obtain training in genomic research. We will also be working with minority institutions to assure that students there receive adequate training in genomic science.

HOW THE HUMAN GENOME PROJECT HELPS TO FIND DISEASE GENES

Mr. Dwyer. The National Center for Human Genome Research (NCHGR) was established on October 1, 1989 in recognition of the growth of the human genome program over the past 2 years. How has the NCHGR incorporated the findings of genes responsible for Cystic fibrosis, Huntington's Disease, and other genomic discoveries?

Dr. Watson. While the searches for genes responsible for such serious human genetic diseases as cystic fibrosis have been successful, they have also been enormously costly and time consuming. The results of the Human Genome Project will facilitate future studies of this type by providing investigators with a much more concrete and detailed base from which to begin their studies. By being able to start with a detailed genetic map and DNA sequence, the identification of the gene--or genes--associated with a specific disease will become much less expensive and progress will be more rapid. This, in turn, will accelerate the research timetable, allowing investigators to get started sooner on the research directed toward understanding the nature of the underlying genetic basis of a disease, how that leads to the manifestation of the disease, and how to control or cure the disease.

COORDINATION WITHIN NIH

Mr. Dwyer. How will the NCHGR coordinate its activities with the ongoing activities of the various National Institutes of Health into gene markers for various inherited diseases?

Dr. Watson. The NCHGR coordinates its research with other institutes in several ways, but primarily through the support of scientific meetings for the express purpose of exchanging information among scientists working in common areas of interest. Specifically, these are: (1) the Human Gene Mapping Workshops which bring together scientists developing genetic and physical maps of the human chromosomes; the purpose of these meetings is to develop consensus maps, to place additional markers on the map, to resolve ambiguities and differences which have been reported and to determine what additional markers are needed in order to achieve an evenly spaced, dense genetic linkage map and (2) the chromosome specific workshops which bring together scientists constructing physical maps of individual chromosomes; these workshops are especially helpful in determining what is needed to achieve a high resolution physical map. In addition, the NIH-DOE Joint Informatics Task Force will be providing guidance about how to collect this information in a timely fashion and make it readily available to the community.

COORDINATION WITH THE DEPARTMENT OF ENERGY

Mr. Dwyer. Explain why the Department of Energy is involved in the mapping of the human genome and how you will coordinate your work so that you will not duplicate your efforts.

Dr. Watson. The Department of Energy has a long-standing program of genetic research for assessing the effects of radiation and energy-related chemicals on human health. DOE's Human Genome Program has three broad objectives that complement the genome research being

conducted by the National Center for Human Genome Research at NIH. These objectives include developing advanced, cost-effective technologies for manipulation and characterization (including sequencing) of DNA; developing new technologies for physical mapping and providing physical maps of all the human chromosomes; and, developing the computer capabilities needed to organize, disseminate, and interpret the vast amount of data generated by the human genome project.

Mechanisms for coordinating the genome activities of NIH and DOE are specified in a 1988 Memorandum of Understanding (MOU). A joint advisory subcommittee was established under the MOU to monitor and coordinate the programs of both agencies. The joint advisory subcommittee will assist the two agencies with the following activities:

o Joint participation in and sponsorship of meetings and workshops for the purposes of planning and review of technical progress, to identify areas of need, and to address general policy questions.

o Development of synchronous calendars for the agencies' research award cycles.

o Concurrent funding and management of selected programs in human genome research that require utilization of the unique NIH or DOE facilities.

o Maintenance of regularly scheduled joint program staff meetings to exchange program information and plans.

o Promotion of the sharing of technological advances and relevant biological materials among investigators supported by both agencies.

o Assurance that relevant data are rapidly placed in appropriate databases.

o Promotion of coordination and exchange of data with other countries.

o Advance sharing of public policy statements relevant to human genome research.

ETHICS WORKING GROUP MEMBERS

Mr. Dwyer. Dr. Watson, you have taken a very aggressive stance to insure that the ethical implications surrounding the mapping of the human genome get a full hearing. Please provide for the record the names and backgrounds of the individuals you have chosen to serve on the Ethics Working Group, and explain your reasons for choosing these particular individuals.

Dr. Watson. The NIH-DOE Working Group on Ethical, Legal and Social Issues Related to Mapping and Sequencing the Human currently

has six members and we expect to appoint some additional members in the next few months. The current member's names, institutional affiliations and backgrounds are as follows:

Nancy S. Wexler, Ph.D.; Hereditary Disease Foundation; College of Physicians and Surgeons of Columbia University; New York, New York. Dr. Wexler is Chairperson of the Working Group and is also a member of the Program Advisory Committee on the Human Genome. She is a clinical psychologist and a biomedical researcher. Her mother died of Huntington's Disease and she is a potential consumer of the information generated by the Human Genome Initiative. Many of her current efforts are to get individuals, interest groups, and the federal government to anticipate how information generated from the Human Genome Initiative can be used to benefit the individual.

Jonathan R. Beckwith, Ph.D.; Harvard Medical School; Boston, Massachusetts. Dr. Beckwith is a bacterial geneticist interested in genetic screening. For more than 20 years, he has been interested in and concerned about the long-range implications of genetics and behavior and genetics and intelligence quotient.

Patricia King, J.D.; Georgetown University Law Center; Washington, D.C. Ms. King is an attorney and academician whose legal career has been in civil rights law. She has served on the National Committee for Protection of Human Subjects, the Recombinant DNA Advisory Committee, and the Presidential Committee on Ethics. Ms. King is a Fellow of the Hastings Center and is interested in genetics and how it affects minorities.

Victor A. McKusick, M.D.; Johns Hopkins Hospital; Baltimore, Maryland. Dr. McKusick is an internationally recognized geneticist who has been active in human genetics research for over 40 years. More than any other person, he has been responsible over the years for collecting data on inherited diseases. Since 1973 he has collected and coordinated data on the human gene map which in 1989 included more than 2,000 genes.

Robert F. Murray, Jr., M.D.; Howard University College of Medicine; Washington, D.C. Dr. R. Murray, Jr. is a clinical researcher who directs a clinical genetics program in sickle-cell disease. He became involved initially with the ethical aspects of screening for sickle-cell disease. Dr. Murray is concerned about individuals who want to plan their destiny based on new technologies emanating from genetics research.

Thomas H. Murray, Ph.D.; Case Western Reserve University; Cleveland, Ohio. Dr. T. Murray is a social psychologist who has written extensively about genetic screening in the work place. He has undertaken fellowships with an emphasis on humanities at Yale University and The Hastings Center. Dr. Murray was recently elected a Fellow of The Hastings Center and is currently co-authoring a publication with a geneticist for the British Medical Association.

These individuals were chosen because they are considered distinguished leaders in their own particular area of research in addition to being knowledgeable about and sensitive to the ethical, legal and social issues surrounding the Human Genome Project.

COMMITMENT TO ETHICAL CONSIDERATIONS

Mr. Dwyer. You have been criticized by some scientists for making such a large commitment to the ethical, legal and social considerations of mapping the human genome. How would you respond to these criticisms?

Dr. Watson. The Human Genome Project is exciting precisely because it is so powerful. The tools created will be of immense benefit to the study of a wide array of human diseases--not to mention agricultural, environmental, and other applications. But we as a society are not accustomed to having so much information about ourselves, in the form of genetic data, available. The medical uses of this information are mainly beneficial, but there are nonmedical uses of genetic information that could be harmful to some individuals. It is essential that as we proceed with the science, we look forward to how its results will be used. The process for anticipating potential problems must involve the scientists doing the work, in addition to humanists and social scientists. Three percent of our budget may or may not prove to be the right amount to spend in this area. Only time and experience will tell. We are committed to spending what is needed to get the job done.

Public funding for biomedical research is premised on a social contract with the public, founded on trust that science will ultimately help people. There are many people worried about how genetic information might be misused, but the issues are diffuse and there are many uncertainties, not only about the science but also about how to think through the issues. The important point is to think forward, and to provide a mechanism to clarify the issues and systematically gather the information and viewpoints needed to resolve them. This will require resources, and if this process prevents the abuse of genetic information in the future, it is money very well spent indeed. As scientists we cannot ignore the impact on society of what we do. Otherwise, we violate the public trust. The budget for examination of ethical, social, and legal implications of genome research is an investment in strengthening that trust.

Mr. Dwyer. What area of human genome research has the potential for being misused the most?

Dr. Watson. Genome research itself presents few novel problems. The concern is not about the research itself, but about applications: how the information generated about human genetics will be used and how technologies that spin off from the project might be misused.

The most immediate concerns are about whether genetic information could be used to discriminate against those who are shown to have a gene associated with a disease. There is potential for employment discrimination, and the availability of genetic tests could result in some people becoming ineligible for various kinds of private insurance. Employers and insurance companies already conduct numerous tests on individuals and genetic tests would add to their ability to evaluate people's health. We will be looking at what new issues will be raised by genetic tests and how to protect people from misuse of such information.

A second concern centers around those who carry a gene that does not cause them harm, but might harm their children if they marry another person who also carries the altered gene. How will their choices about having children and obtaining health care for them be affected by public polices?

Another concern centers on those who are found to carry a gene that predicts with great likelihood that they will become disabled later in life. They are health now but may become disabled. Genetic tests introduce the possibility of knowing this predisposition in advance with greater certainty than is possible with currently available tests.

The prototypical case is testing for Huntington's disease. It became possible a few years ago to test individuals in some families. The test is roughly 95 to 98 percent reliable at predicting whether one will develop Huntington's disease later in life. Many, in fact most, people at risk of developing Huntington's disease have declined the opportunity to take this test. The dilemma comes with how to handle those who do take it. The most common reasons to take the test are to help individuals make decisions about whether to have children, about financial and life plans, or just to know for sure one way or the other. This is an agonizing private choice. The uncertainties come when such information is sought by employers or private insurance companies.

Should an airline pilot who knows he or she has the Huntington's gene be obligated to report that to the airline or the FAA? Should private companies who wish to reduce their health insurance, life insurance, and sick leave costs be allowed to discriminate against such persons, by refusing to hire them or proceeding to fire them? Should employers even be allowed to ask if a person has taken the test? It seems inherently unfair for information intended to assist individuals to be turned against them. If individuals know they are likely to die young or to become disabled, however, then they have a strong incentive to buy lots of life insurance or disability insurance. A few such individuals can financially ruin private insurers who base their actuarial projections on population averages. Many private insurers in fact went out of business earlier in this century because of this problem, and many who had bought insurance never reaped the benefits or secured any protection. It is dilemmas such as these that cry out for creative thinking.

None of the problems is entirely new, nor are genetic tests unique in raising these issues. There are laws that say what information can and cannot be used by employers. The Americans with Disabilities Act, currently pending in the House of Representatives, could be extended to cover unfair genetic discrimination, for example. Private insurers already use nongenetic and genetic medical information in making their decisions about whom to insure and how much to charge. Genetic tests are merely a new arena in which to deal with problems confronted elsewhere in medicine. I am confident that we can come up with new public policies to deal with these problems, but it will take careful thought and extensive public debate.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

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NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

For carrying out section 301 and Title IV of the Public Health Service Act with respect to human genome research, [$60,000,000] *$108,029,000*.

(Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 1990.)

National Center for Human Genome Research

Language Analysis

Language Provision	Explanation
"For carrying out section 301 and Title IV of the Public Health Service Act with respect to human genome research..."	These activities were formerly part of the National Institute of General Medical Sciences and the Office of the Director, NIH. These activities were organizationally combined into the National Center for Human Genome Research on October 1, 1989 and funds were appropriated by Congress as a separate account under P.L. 101-166.

NATIONAL INSTITUTES OF HEALTH

NATIONAL CENTER FOR HUMAN GENOME RESEARCH

Amounts Available for Obligation 1/

	1989 Actual	1990 Appropriation	1991 Estimate
Appropriation	---	$60,000,000	$108,029,000
Enacted administrative reduction	---	-62,000	---
Sequester order	---	-400,000	---
Subtotal, adjusted appropriation	---	59,538,000	108,029,000
Comparative transfer from:			
The National Institute of General Medical Sciences for the human genome research program	+27,569,000	---	---
The Office of the Director, NIH, for administrative costs of the human genome research program	+661,000	---	---
Subtotal, adjusted budget authority	28,230,000	59,538,000	108,029,000
Total, obligations	28,230,000	59,538,000	108,029,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: FY 1990 - $100,000 and FY 1991 - $104,000.

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

Budget Mechanism
(Dollars in thousands)

	1989 Actual		1990 Appropriation		1991 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research grants:						
Research projects:						
Noncompeting	60	$16,273	94	$24,486	117	$34,916
Admin. supplementals				700		
Competing:						
Renewal	4	934	6	1,818	25	8,328
New	37	9,502	44	13,342	28	9,328
Subtotal, competing	41	10,436	50	15,160	53	17,656
Subtotal, res. proj	101	26,709	144	40,346	170	52,572
Research centers:						
Specialized/comp. centers	--	300	3	7,947	9	35,738
Other research:						
Research career programs	--	--	6	401	12	850
Other research related	1	37	10	993	18	1,800
Subtotal, other research	1	37	16	1,394	30	2,650
Total, research grants	102	27,046	163	49,687	209	90,960

Training:						
Individual awards:						
Noncompeting	--	--	--	--	50	1,290
Competing:						
New	--	--	50	1,242	25	646
Subtotal, individual	--	--	50	1,242	75	1,936
Institutional awards:						
Noncompeting	--	--	--	--	85	1,785
Competing:						
New	--	--	85	1,738	64	1,345
Subtotal, institutional	--	--	85	1,738	149	3,130
Total, training	--	--	135	2,980	224	5,066
Research and development contracts	--	500	4	4,730	5	7,971
	FTEs		FTEs		FTEs	
Research management and support	3	684	30	2,141	38	4,032
Total	3	28,230	30	59,538	38	108,029

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

CROSSWALK - 1989 Actual

(Dollars in thousands)

PROGRAM ACTIVITY	MECHANISM							
	Research Grants			Training Programs		Research and Development Contracts	Research Management and Support	Total
	Research Projects	Research Centers	Other Research	Individual	Institutional			
Human genome research.....	$26,709	$300	$37			$500		$27,546
Research management and support.....							$684	684
Total.....	26,709	300	37			500	684	28,230

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

CROSSWALK - 1990 Appropriation

(Dollars in thousands)

PROGRAM ACTIVITY	MECHANISM							
	Research Grants			Training Programs		Research and Development Contracts	Research Management and Support	Total
	Research Projects	Research Centers	Other Research	Individual	Institutional			
Human genome research.....	$40,346	$7,947	$1,394	$1,242	$1,738	$4,730		$57,397
Research management and support.....							$2,141	2,141
Total.....	40,346	7,947	1,394	1,242	1,738	4,730	2,141	59,538

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

CROSSWALK - 1991 Estimate

(Dollars in thousands)

PROGRAM ACTIVITY	MECHANISM							
	Research Grants			Training Programs		Research and Development Contracts	Research Management and Support	Total
	Research Projects	Research Centers	Other Research	Individual	Institutional			
Human genome research.....	$52,572	$35,738	$2,650	$1,936	$3,130	$7,971		$103,997
Research management and support.....							$4,032	4,032
Total.....	52,572	35,738	2,650	1,936	3,130	7,971	4,032	108,029

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

Summary of Changes

1990 Estimated budget authority	$59,538,000
1991 Estimated budget authority	108,029,000
Net change	+48,491,000

	1990 Current Estimate Base		Change from Base	
	Pos. FTEs	Budget Authority	Pos. FTEs	Budget Authority
CHANGES:				
A. Built-in:				
1. Within grade increases		$ 1,432,000		+16,000
2. Annualization of January 1990 pay raise		1,432,000		+3,000
3. One extra day of pay		1,432,000		+6,000
4. January 1991 pay raise		1,432,000		+58,000
5. Increased costs of supplies, materials and other research management support activities		709,000		+17,000
Subtotal				+100,000

B. Program:	No.	Amount	No.	Amount
1. Research project grants:				
a. Noncompeting	94	$25,186,000	+23	+9,730,000
b. Competing	50	15,160,000	+3	+2,496,000
Total	144	40,346,000	+26	+12,226,000
2. Research centers	3	7,947,000	+6	+27,791,000
3. Other research:				
a. Careers	6	401,000	+6	+449,000
b. Other research related	10	993,000	+8	+807,000
Total	16	1,394,000	+14	+1,256,000
4. Research Training				
a. Individual	50	1,242,000	+25	+694,000
b. Institutional	85	1,738,000	+64	+1,392,000
Total	135	2,980,000	+89	+2,086,000
5. Research and development contracts	4	4,730,000	+1	+3,241,000
6. Research mangement and support	30	$2,141,000	+8	+1,791,000
Subtotal				+48,391,000
Total changes				+48,491,000

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

Budget Authority by Activity
(Dollars in thousands)

	1989 Actual		1990 Appropriation		1991 Estimate	
	FTEs	Amount	FTEs	Amount	FTEs	Amount
Human genome research		$27,546		$57,397		$103,997
Research management and support	3	684	30	2,141	38	4,032
Subtotal, obligations		28,230		59,538		108,029
Total, budget authority	3	28,230	30	59,538	38	108,029

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

Budget Authority by Object

	1990 Appropriation	1991 Estimate	Increase or Decrease
Total number of full-time permanent positions	45	45	--
Total compensable work years:			
Full-time equivalent employment	30	38	+8
Full-time equivalent of overtime and holiday hours	1	1	--
Average ES salary	$76,400	$90,200	+$13,800
Average GM/GS grade	9.8	9.8	--
Average GM/GS salary	36,671	37,964	+1,293
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	51,350	53,160	+1,810
Personnel compensation:			
Full-time permanent	$1,197,000	$1,777,000	+580,000
Other than full-time permanent	58,000	85,000	+27,000
Other personnel compensation	5,000	8,000	+3,000
Total, personnel compensation	1,260,000	1,870,000	+610,000
Personnel benefits	172,000	255,000	+83,000
Travel and transportation of persons	116,000	120,000	+4,000
Transportation of things	1,000	1,000	---

	1990 Appropriation	1991 Estimate	Increase or Decrease
Rent, communications, and utilities	42,000	44,000	+2,000
Printing and reproduction	5,000	5,000	---
Other services:			
Project contracts	4,730,000	7,971,000	+3,241,000
Other	362,000	1,510,000	+1,148,000
Supplies and materials	13,000	13,000	---
Equipment	170,000	214,000	+44,000
Grants, subsidies & contributions	52,667,000	96,026,000	+43,359,000
Total	59,538,000	108,029,000	+48,491,000

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

Significant Items in House and Senate Appropriations Committee Report

Item	Action taken or to be taken
1990 House Report	
1. "The Genome project is an expensive but extraordinarily promising area of biomedical research. The Committee will expect a comprehensive spending plan prior to hearings on the 1991 budget." (page 84)	A five-year plan for the Human Genome Project was developed jointly by the NIH and the Department of Energy. This plan outlines specific goals for the period FY 1991 through FY 1995.
1990 Senate Report	
1. "The Committee understands that NIH has proposed to transfer responsibility for directing this rapidly growing project to the new National Center for Human Genome Research, the creation of which is currently awaiting departmental approval. The Committee intends to await a request and recommendation on this matter before taking action to transfer this program out of the NIGMS." (page 134)	The National Center for Human Research was established by the Secretary on October 1, 1989 and the Congress appropriated FY 1990 funds to the NCHGR as a separate account.

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1990 Amount Authorized	1990 Estimate	1991 Amount Authorized	1991 Budget Estimate
Research and Investigation	Section 301	42a241	Indefinite	$56,558,000	Indefinite	$102,963,000
National Research Service Awards	Section 487(d)	42a288	Such sums as necessary 1/	2,980,000	Authorizing legislation to be requested	5,066,000
Total Budget Authority				59,538,000		108,029,000

1/ This training authority is shared with other research training program of the National Institutes of Health and the Alcohol, Drug Abuse, and Mental Health Administration.

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

Appropriations History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1990	$100,000,000	$62,000,000	--- 1/	$59,938,000 2/
1990 Sequester				-400,000
1991	108,029,000			

1/ The Senate did not provide funds for the National Center for Human Genome Research; however, the Senate allowance included $61,847,000 for the Human Genome Initiative within the National Institute of General Medical Sciences' account.

2/ Excludes enacted administrative reduction of $62,000.

Justification

National Center for Human Genome Research

	1990 Appropriation		1991 Estimate		Increase or Decrease	
	FTEs	BA	FTEs	BA	FTEs	BA
NCHGR	30	$59,538,000	38	$108,029,000	8	$48,491,000

General Statement

The National Center for Human Genome Research (NCHGR) was created with the primary mission of mapping the human genome and sequencing the human DNA. The data and the technology emanating from this program will be key tools in biology in the 21st century. The genetic messages encoded within our DNA molecules constitute the basic instructions for the chemical foundation of human existence. By determining the location and structure of specific genes on the 23 pairs of human chromosomes, scientists will gain valuable tools to use in their quest to understand and eventually treat many of the more than 4,000 single-gene diseases that afflict mankind, as well as the many multi-factorial diseases in which genetic predisposition plays an important role. The information generated will also have a profound impact on many other fields of science and technology.

The NCHGR was established on October 1, 1989. The center evolved in recognition of the growth of the human genome program over the last 2 years and the high priority NIH and the Administration place on this basic research initiative. The center was created by combining the functions of the Office of Human Genome Research, a planning and coordinating unit within the Office of the Director, NIH, and the human genome grants and contracts management previously provided by the National Institute of General Medical Sciences.

During FY 1990, a five-year plan for the Human Genome Project was developed jointly by the National Institutes of Health (NIH) and the Department of Energy (DOE), in consultation with the NIH Program Advisory Committee on the Human Genome and the DOE Health and Environmental Research Advisory Committee (HERAC). The plan outlines specific program goals for the period FY 1991 through FY 1995. The goals are:

Mapping and sequencing the human genome

Complete a fully connected human genetic map with markers spaced an average of two to five centimorgans apart.

Assemble physical maps of all human chromosomes with the goal of having markers spaced at approximately 100,000 base pair intervals.

Generate continuous overlapping sets of cloned DNA or closely spaced unambiguously ordered markers covering lengths of at least 2 million base pairs for large parts of the human genome.

Determine the sequence of an aggregate of 10 million base pairs of human DNA in large continuous stretches in the course of technology development and validation.

Improve current methods and/or develop new methods for DNA sequencing that will allow large scale sequencing of DNA at a cost of $0.50 per base pair.

Model organisms

Prepare a genetic map of the mouse genome based on DNA markers. Start physical mapping on one or two mouse chromosomes.

Sequence an aggregate of 20 million base pairs of DNA from a variety of model organisms, focusing on stretches that are one million base pairs long. This sequencing will be done in conjunction with the development and validation of new and/or improved DNA sequencing technologies.

Informatics--Data collection and analysis

Develop effective software and database designs to support large-scale mapping and sequencing projects.

Create database tools that provide easy access to up-to-date physical mapping, genetic mapping, chromosome mapping, and sequencing information and allow ready comparison of the data in these several data sets.

Develop algorithms and analytical tools that can be used in the interpretation of genomic information.

Ethical and legal considerations

Develop programs addressed at understanding the ethical and legal implications of the Human Genome Project.

Identify and define the major ethical and legal issues and develop policy options to address them.

Research Training

Support research training of pre- and post-doctoral fellows starting in FY 1990. Increase the number of trainees supported until a constant number of approximately 600 full-time trainee positions is attained.

Examine the need for other types of research training in the next year.

Technology development

Support innovative and high risk, high payoff technological developments as well as improvements in current technology to meet the needs of the genome project.

Technology transfer

Enhance the already close working relationships with U.S. industry.

Encourage and facilitate the transfer of technologies and of medically important information to the medical community.

These five-year goals are presented with some specificity; however, recognizing that substantial progress has been made in technology development in the past 2 years, it must be stressed that the next 5 years will still be a time in which rapid advances in methods and strategies will be necessary if the program is to meet the goals outlined. Extreme flexibility and diligence on the part of program management, for both the research and its administration, will be needed during this period of research and technological development. Consequently, the plan will be updated annually.

Overall Budget Policy

The FY 1991 budget request for the National Center for Human Genome Research is $108,029,000. This amount represents an increase of $48,491,000 or 81.5 percent over the comparable FY 1990 estimate and reflects the high priority accorded this initiative by the Administration. The research supported will be entirely basic research.

The FY 1991 budget request for research project grants is $52,572,000. This level will support 117 noncompeting research project grants at an average cost of $298,000, and 53 competing research project grants at an average cost of $333,000--a total increase of 26 research project grants over the FY 1990 estimate. On average, research project grants will receive an increase of 10.4 percent compared to FY 1990 estimates.

The FY 1991 request for research centers is $35,738,000. This level will support nine specialized research centers, six more than in FY 1990.

The NCHGR expects to fund approximately 30 other research-related awards at a level of $2,650,000. This includes 12 research career awards at a level of $850,000 and 18 conference or other research awards at a level of $1,800,000. This represents an increase of 14 awards over FY 1990 estimates.

Support for research training grants will increase approximately 70 percent over FY 1990. The NCHGR anticipates supporting 75 individual fellowships and 149 full-time training positions under 24 institutional training grants for a total of 224 trainees at a level of $5,066,000.

Five cooperative research and development contracts and continued support of NIH intramural scientists will be funded at a level of $7,971,000. This is an increase of $3,241,000 over the FY 1990 estimate.

The FY 1991 request provides $4,032,000 for research management and support activities, an increase of $1,891,000 over the FY 1990 estimate. This increase represents built-in increases for pay-related costs, new charges for centrally furnished services, and increased or new costs of services and supplies. Additional increases are for salaries and related expenses for additional full-time equivalent positions which are needed to manage the expanded program.

Program Accomplishments

Genetic Linkage Map

Gene mapping is the determination of the relative order of genes on chromosomes. A genetic linkage map places one gene or marker relative to another on the basis of how often they are inherited together. The linkage strategy of genetic mapping exploits the way chromosomes are transmitted from one generation to the next. During the process of egg or sperm formation, the chromosomes are duplicated and exchange or "recombination" occurs between homologous regions on different chromosomes. The amount of recombination between two genes depends on how far apart the genes are from one another. The farther apart the genes, the more likely the two are to be separated by recombination. Such recombination events can be measured experimentally and analyzed mathematically to determine relative location and distance between genes or markers. Linkage maps generated in this way are described in units of distance called centimorgans; one centimorgan is defined as a one percent chance that one genetic locus is separated from another as they are transmitted from one generation to the next.

A dense genetic linkage map, with markers spaced an average of two to five centimorgans apart, would be a very valuable tool for use in identifying the location of particular genes of interest, especially those for which the chemical product is unknown. Primary among the latter are altered genes that cause genetic diseases. To produce such a linkage map is one of the goals of the Human Genome Project. The laboratories of Dr. Helen Donis-Keller and Dr. Raymond White have played a significant role in the development of the current human linkage map.

Dr. Donis-Keller, initially at Collaborative Research, Inc., and more recently at Washington University, is working to construct a linkage map of the human genome with markers spaced five centimorgans apart. Since her original publication in 1987, which identified approximately 400 markers, 150 new markers have been added to the map. This brings the total number of useful markers mapped by Dr. Donis-Keller to 550 and represents an average marker spacing of approximately 6 centimorgans. However, the distribution of mapped markers is not uniform and there are still many regions of the genome in which the spacing of markers is considerably greater than 10 centimorgans. Filling these gaps is a major aim of current genetic linkage mapping efforts.

Dr. White, at the University of Utah, has turned his efforts towards chromosomes in which there is a paucity of markers relative to the average density of markers on the human map. At present, these efforts focus on chromosomes 16, 17 and 19. Dr. White is also working on the development of new types of genetic markers and on linking the genetic map and the physical map. He is collaborating in this work on chromosome 16 with workers at the Los Alamos National Laboratory.

Through the efforts of an international research collaboration, organized by the Centre d'Etudes des Polymorphismes Humaines (CEPH), the genetic mapping data from many other laboratories can be combined with those of large-scale efforts such as Dr. White's and Dr. Donis-Keller's to produce high density

"consortium" genetic maps of individual chromosomes. The NCHGR has supported meetings among the CEPH collaborators studying individual chromosomes in order to expedite the production of these consortium maps.

Sequence-Tagged Sites (STS) Consensus Map Proposal

As noted above, genetic maps describe gene order in terms of recombination frequency, or genetic distance. Another useful type of genome map is known as a physical map, in which the distance between genes is measured by the number of nucleotides--the chemical components of DNA--between the genes. There is a large and increasing number of techniques available for measuring physical distances on DNA. Until recently, physical maps constructed by different techniques were hard to compare with one another. However, a major conceptual breakthrough in human genome research that addressed this problem is the proposal for a map consisting of a set of sequenced-tagged sites (STS's). This proposal was first published in the summer of 1989. STS's are defined as short stretches of DNA sequence that uniquely define a region of DNA and can be mapped by many available techniques. The data generated from laboratories using different techniques can then be related using STS identifiers and the tagged markers can be placed together on a single physical map. Because an STS uniquely defines a particular chromosomal region and allows a scientist to readily reisolate this region, as needed, use of these identifiers will reduce the need to store and disseminate cloned DNA segments from a long-term central repository and will facilitate the sharing of research results.

During 1990, the STS concept will have been refined, specific criteria for the definition of an STS will have been developed, and a pilot program for converting existing markers to STS will have been designed. Topics which will have been addressed include, the adoption of STS standards, a plan to ensure quality control, and a plan for a central STS database.

DNA Sequencing

During the past year, work from at least four laboratories has significantly improved the rate at which DNA sequencing can be done using existing DNA sequencing machines. For example, Dr. Leroy Hood at the California Institute of Technology, obtained 70,000 base pairs of "finished" sequence--DNA that has been sequenced at least five times to ensure the accuracy of the final sequence--in seven months. By increasing the capacity of each machine, using improved computer programs for analysis, and automating the isolation, preparation and loading of the DNA onto the machines, Dr. Hood expects that his laboratory will be able to double its output of finished sequence within one year and increase the rate seven-fold in three years. This could result in a rate of about 56,000 finished base pairs of DNA sequence per machine per week, compared with 8,000 base pairs per week currently possible.

In addition to supporting work directed toward improving automated DNA sequencing machines, a number of attempts to develop completely new technologies for DNA sequencing have been funded by the NCHGR. For example, Dr. Thomas Brennan from Genomyx, Inc. has demonstrated the feasibility of using capillary gels to separate DNA and to determine DNA sequence using mass

spectroscopy. The advantage of this method is that sequence can be determined very quickly and the capillary gels can be produced in large numbers and stored for long periods of time.

In another approach to increasing the efficiency of DNA sequencing, several laboratories, both academic and industrial, are developing automated film scanners that can accurately read X-ray films containing DNA sequence. Development of a reliable film scanner would greatly increase the speed of reading the DNA sequence from X-ray films used in conventional sequencing and in turn benefit both large and small-scale sequencing efforts.

Mapping and Sequencing the DNA of Model Organisms

Genomic studies of bacteria, yeast, the fruit fly, simple worms, the mouse, and other experimental organisms are important for several reasons. Such studies will add significantly to our understanding of the human genome because more is known about the molecular biology of these organisms than about human molecular biology and the information gained from the study of model organisms can often be applied to the human. Simple model organisms can also serve as useful systems for technology development. Information about the genomic structure of non-human systems will also have useful ramifications in important non-medical areas such as agriculture, biotechnology, and waste management.

Useful physical maps of the genomes of two important model organisms, the yeast S. cerevisiae and the roundworm C. elegans are close to completion. However, the construction of complete physical maps of complex genomes is not yet routine and improved strategies and technologies are needed. The development of yeast artificial chromosome (YAC) vectors as a vehicle for cloning DNA fragments offers the possibility of simplifying the construction of physical maps. Dr. Daniel Hartl from the Washington University School of Medicine is constructing a physical map of the fruit fly genome using this technology.

In initial studies, Dr. Hartl was able to show that the YAC vectors contained faithful copies of DNA segments, that both unique and repeat sequences were clonable, and that large pieces of DNA could be cloned in one piece. YAC clones are expected to be very useful in the development of complete physical maps of the human genome.

Data collection and distribution

The final product of the Human Genome Project will be a database containing a mosaic of sequences from many sources representing the entire human genome. Several groups are currently working on the development of new database structures and concepts needed to handle the vast amount of data to be generated by the project. The current DNA sequence database, GenBank, has recently undergone a restructuring that will begin to address the problems it will face as the amount of new data submitted increases. Until recently, distribution of data from GenBank was on a quarterly basis. Timely access to the most recent data is essential to a researcher who has just determined a sequence in order to investigate whether there is a relationship between the new sequence and one that has already been deposited in the database. When this type of similarity is found, it provides the researcher with important

information about the possible function of the new sequence. In response to the community's need for rapid access to new data, the NCHGR provided funds to the National Institute of General Medical Sciences (NIGMS) to help support an online service to the GenBank computer. Using this service, investigators now have immediate access to a database that is updated daily.

Ethical and Legal Considerations

The use of genetic information has many ethical and legal implications for individuals and society. Therefore, any scientific endeavor of this magnitude must be accompanied by a plan to ensure that the public is informed about how this information can be used positively to diagnose and eventually treat genetic diseases and other medical conditions. In addition responsible policies must be developed to anticipate and prevent any adverse use of this information.

The Ethics Working Group, a subcommittee of the Program Advisory Committee on the Human Genome, has made significant progress in developing a plan that will attempt to anticipate the impact of the Human Genome Project and address what protection needs to be in place so that the information generated from the Human Genome Project can be of maximum benefit to individuals and society. The Ethics Working Group has developed a four-point agenda to:

(1) Stimulate research by encouraging investigators to explore a wide range of pertinent issues.

(2) Refine the research agenda by discussion with experts in the fields and by periodically collecting additional information through small workshops, commissioned papers, and invited speakers from various fields.

(3) Solicit public input from the general public. Town meetings will be held to educate the general public and to solicit their questions and concerns about human genome research and how this information might be used.

(4) Support education through developing materials, both formal and informal, targeted at patients, students at all educational levels, teachers, the media, medical practitioners, genetic counselors, and scientists.

Technology Development

The NCHGR continues to fund projects which will advance the technology needed to complete the Human Genome Project. As an example, Dr. David Ward, at Yale University, is developing a technique to isolate large fragments of DNA by direct physical means using a combination of hybridization and affinity chromatography techniques as a way to increase the size of DNA fragments that can be readily isolated. This approach should result in the preparation of specific DNA fragments in amounts needed for conducting experiments by a procedure which is simpler than current cloning techniques.

A major outcome of the Human Genome Project will be a variety of DNA diagnostics. At the California Institute of Technology, Dr. Leroy Hoods' laboratory has already devised a method using the powerful polymerase chain

reaction technique to detect single base changes in the DNA of a specific gene. Using this method, large numbers of patients could be quickly screened for a genetic difference or mutation.

Expanded Research Mechanisms

The NCHGR expanded the use of extramural mechanisms in FY 1990 to include, in addition to investigator-initiated research project grants, the following grant mechanisms.

Research Centers were initiated in FY 1990. These centers were established so that groups of 15 to 20 researchers from several disciplines can pool their talents. The research supported in each center is tightly focussed on a specific goal of the Human Genome Project. These centers differ from other large genome research efforts in that they must be the foci for collaboration with other investigators, for sharing and distributing materials, and for data collection on a national or international scale.

Research Career Awards will provide newly established scientists the opportunity to dedicate a significant amount of their time to the human genome research effort in order to accelerate research in their own area of interest. The type of research required for completion of the Human Genome Project will demand the concentrated effort and creativity of scientists from a variety of scientific disciplines.

Research Training programs are being established to train scientists who can integrate mathematical, physical, chemical, engineering, and/or computer sciences with molecular biology and genetics. This type of interdisciplinary training is necessary for the successful completion of the project.

Intra-agency Agreements between the NCHGR and the other Institutes of the National Institutes of Health were established in order to provide co-funding to intramural scientists who wish to expand their work on projects that contribute to the Human Genome Project. We anticipate significant contributions from the outstanding scientists employed by the National Institutes of Health.

These mechanisms of support will play an increasingly important role as the human genome program evolves.

National Center for Human Genome Research

Human Genome Research

1991 Authorization: Indefinite

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$57,397,000	$103,997,000	$46,600,000

Purpose and Method of Operations

The possibility of knowing the complete set of genetic instructions of the human or other organisms seemed an unreachable scientific goal when the chemical structure of DNA was discovered a mere 35 years ago. Today new techniques have enabled scientists to isolate individual genes, to chop up DNA at identifiable and predictable points, to mix and match pieces of DNA in various organisms, to grow unlimited quantities of these fragments in bacteria, and, in general, to take DNA apart and put it back together again in designed ways. They have learned to make DNA from laboratory chemicals. Scientists have also learned to "sequence" DNA, that is, determine the order in which the four chemical components, called A, T, C, and G occur and to note its tiniest variations. Breakthroughs in recombinant DNA technology have now made the sequencing of short stretches of DNA a routine laboratory procedure. However, technology is still inadequate for the sequencing of long stretches of DNA.

The human genome consists of 50,000 to 100,000 genes located on 23 pairs of chromosomes. Mapping and sequencing both the human genome and those of other so-called "complex model organisms" is expected to yield information that will have a dramatic impact on our understanding of human biology and genetic diseases and that should accelerate the search for both cures and preventive measures for these conditions.

Rationale for the Budget Request

The FY 1991 budget request is $103,997,000, an increase of $46,600,000 over the FY 1990 estimate. This level will support 209 research grants, 224 full-time trainee positions, 5 research and development contracts, and support to NIH intramural scientists working on human genome research. The following are program plans for FY 1991.

Genetic Linkage Maps

One of the goals of the Human Genome Project is to produce a human genetic linkage map with markers spaced an average of two to five centimorgans apart. The challenge is to get markers evenly spaced along each of the chromosomes. An important strategy for this research is for the new markers to be on the same segments of DNA that were used by other researchers to construct physical maps, thus making it easier to correlate the genetic linkage map with the physical maps produced in other laboratories.

In addition to funding individual research projects, the NCHGR will continue to use the conference grant mechanism to bring together researchers from different laboratories who are conducting genetic linkage studies to develop composite maps of each chromosome. Activities of this type facilitate the exchange of information, eliminate unnecessary duplication of research efforts, define the areas where more markers are needed, and resolve experimental differences.

Planning and Implementing a Sequence-Tagged Site Consensus Map

Scientists involved in mapping the human genome use a variety of methods to produce maps with different levels of resolution. One of the difficulties is the ability to integrate the information derived from two different types of maps. This problem could be resolved by using a system of identifying short unique DNA sequences to characterize each piece of DNA that is mapped on the chromosome. These "sequence-tagged sites" (STS) can be generated by researchers regardless of which different mapping techniques they use. Because the proposal has many advantages from a scientific and management point of view, the plan for construction of a consensus physical map based on the concept of sequence-tagged sites will be implemented.

DNA Sequencing

During FY 1991 research efforts will focus on refining the genetic and physical maps of the human genome. Sequencing efforts will be limited to pilot projects where large regions of DNA coding for known functions will be sequenced. These pilot efforts are particularly important because they will provide information as to which approaches will make large scale sequencing feasible. In the process, new biological insight will be gained about interesting human loci. Currently pilot projects of this type are sequencing the T-cell receptor locus--thought to be involved in multiple sclerosis and numerous other diseases--and the c-abl oncogene.

In model systems, major progress in the DNA sequencing of the bacterium Escherichia coli (E. coli) is expected as well as initiation of DNA sequencing of other model organisms whose genomes are small and well mapped. Continued funding of DNA sequencing in model organisms is essential not only for feasibility studies but also because of the insights it provides into understanding the human DNA sequence. For example, by knowing the DNA sequence at the ends of chromosomes from Tetrahymena (an invertebrate organism) investigators have been able to isolate the DNA sequence that

characterizes the ends of human chromosomes. This type of breakthrough would not have been possible for several more years if the information from the model organism had not been available.

Informatics--data collection and analysis

With the help of the recently established NIH/DOE Joint Informatics Task Force, a plan will be developed for meeting the informatics needs of the human genome project and grants and contracts appropriate to this plan will be funded. Both data management needs and data analysis needs will be addressed. Much of the informatics work will be conducted as an integral part of the research projects described in other sections of this document, but some efforts will also receive separate funding. A primary goal will be to develop the capability to make the data generated by the Human Genome Project readily accessible to all who need the data.

Ethical and Legal Considerations

The knowledge gained from research on the human genome will have profound effects on individuals and society. Although the results may be several years away, it is important that individuals be informed about the program and have an opportunity to participate in discussions. In FY 1991, a series of town meetings will be held in several locations throughout the United States to inform individuals about the Human Genome Project and to solicit their concerns about human genome research.

There are many issues which must be addressed and a thorough examination of these along with the development of a series of options and recommendations will be essential. In FY 1991, meetings will be held to bring together individuals from several different disciplines, such as religion, law, ethics, and industry to address key issues and develop recommendations. In addition, grants for scholarly work which examines these issues in detail will be awarded.

Research Training

To accomplish the goals of the Human Genome Project, highly trained scientists will be needed in a variety of scientific disciplines. The NCHGR will continue the pre-doctoral and post-doctoral training programs which prepare highly qualified individuals to engage in research relevant to the genome project. The center is particularly interested in training highly qualified scientists who are able to: (1) integrate mathematical, physical, chemical, engineering, and/or computer sciences with molecular biology and genetics; and (2) use those interdisciplinary skills to develop research programs in the mapping and sequencing of the human genome and the genomes of other organisms, as well as in the analysis of the resulting data and the development of medical or biotechnological applications based on the data.

In addition, post-doctoral fellowships will be offered to train individuals who wish to study the ethical and/or legal issues related to the Human Genome Project.

Technology Development

Many of the current techniques used in the Human Genome Project have been developed by scientists who were interested in studying only one small portion of a chromosome or a specific gene. To continue to use these same techniques to pursue a project which is more than a thousand times larger would be inefficient and would take more than the projected 15 years. Therefore, the success of the Human Genome Project depends on the development of new or the automation of existing technologies, the simplification of procedures, and the reduction of the costs involved. In 1991, the NCHGR will continue to support projects in technology development that have the potential to accelerate research on the human genome.

National Center for Human Genome Research

Research Management and Support

1991 Authorization: Indefinite

Budget Authority:

1990 Appropriation		1991 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA
30	$2,141,000	38	$4,032,000	8	$1,891,000

Purpose and Method of Operations

The Research Management and Support activity provides staff and resources for the program management and scientific direction of the National Center for Human Genome Research.

The Office of the Director provides overall guidance and professional leadership needed to manage the human genome program. The Office of Information and Legislative Affairs provides coordination and information dissemination to the Congress, the press and others. The Office of Administrative Management includes financial management, human resources management, grants and contracts administration, information resources management, as well as providing general administrative services to the center.

The Division of Extramural Programs provides policy direction and coordination for all phases of scientific and technical review activities involving research grants, research training grants, and research and development contracts. The extramural program staff plans, develops, and monitors center activities and serves as liaison with applicants, grantees, other components of NIH and the Department, advisory bodies and other interested groups.

Rationale for the Budget Request

The FY 1991 request provides $4,032,000 for research management and support activities, an increase of $1,891,000 over the FY 1990 estimate. This increase represents built-in increases for pay-related costs, new charges for centrally furnished services, and increased or new costs of services and supplies. Additional program increases for salaries and related expenses for additional full-time equivalent positions needed to manage the expanded program.

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

Detail of Permanent Positions

	1989 Actual	1990 Appropriation	1991 Estimate
ES-4	1	1	1
Subtotal	1	1	1
GS/GM-15	1	3	3
GS/GM-14		7	7
GS/GM-13		5	5
GS-12		7	7
GS-09	1	3	3
GS-08		1	1
GS-07	1	9	9
GS-06		2	2
GS-05		5	5
GS-02	--	1	1
Subtotal	3	43	43
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Full Grade	--	1	1
Subtotal	--	1	1
Total permanent positions	4	45	45

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NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

Advisory and Assistance Services

The National Center for Human Genome Research was established on October 1, 1989, and appropriated as a separate account. During FY 1990, the center expects to host and/or sponsor a variety of conferences and/or workshops. Additionally, we will be supporting the Program Advisory Committee on Human Genome. For FY 1991, the Advisory and Assistance Services budget is $265,000, a modest increase of $8,000 over the comparable FY 1990 level.

The conferences and workshops sponsored/hosted by the center will have two different areas of emphasis. Some meetings will be held to bring together investigators with common research objectives and to encourage collaboration, exchange of materials and use of common starting materials or protocols where these are appropriate. Other meetings will be held to bring together individuals from several different disciplines, such as religion, law, ethics, and industry to address key issues, develop recommendations, and suggest strategies for informing the public about genome research and its potential benefits.

The personnel appointment mechanism is used to support the Program Advisory Committee on the Human Genome. The Advisory Committee is expected to meet three times yearly to provide overall guidance to the NIH. The committee has representatives from industry and academia as well as a member representing the area of ethics. The Committee represents the broad range of scientific expertise needed to oversee the Human Genome Project.

Internal control policy guidelines exist in the form of OMB Circular A-120, Guidelines for the Use of Advisory and Assistance Services, and DHHS General Administrative Manual 8-15, Advisory and Assistant Services. This guidance has been promulgated to make staff aware of the definition of Advisory and Assistance Services (AAS). The NIH Accounting System contains Common Accounting Numbers (CAN's) that have been designated for use in identifying and aggregating costs for AAS. Additionally the center has established a review process involving all appropriate administrative and management personnel. Proposals are reviewed by the Administrative Officer, the Committee Management Officer, the Budget Officer, the Executive Officer, appropriate branch managers, and the Deputy Director, as necessary.

TUESDAY, MARCH 20, 1990.

JOHN E. FOGARTY INTERNATIONAL CENTER FOR ADVANCED STUDY IN THE HEALTH SCIENCES

WITNESSES

DR. PHILIP E. SCHAMBRA, DIRECTOR, FOGARTY INTERNATIONAL CENTER
DR. WILLIAM F. RAUB, ACTING DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. RICHARD M. KRAUSE, SENIOR SCIENTIFIC ADVISOR, FOGARTY INTERNATIONAL CENTER
DR. CORALIE FARLEE, ASSISTANT DIRECTOR FOR PLANNING AND EVALUATION, FOGARTY INTERNATIONAL CENTER
WILLIAM M. DOAK, EXECUTIVE OFFICER, FOGARTY INTERNATIONAL CENTER
ELLA L. MENSER, BUDGET OFFICER, FOGARTY INTERNATIONAL CENTER
DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. NATCHER. Now we take up the John E. Fogarty International Center as our next item of the committee. Dr. Schambra is the Director.

Dr. Schambra, before you give us your statement, tell us who you have with you there at the table.

Dr. SCHAMBRA. Thank you, Mr. Chairman. On my far left is Ms. Ella Menser, our Budget Officer. To her right is Mr. William Doak, our Executive Officer. To my immediate left is Dr. Coralie Farlee, our Assistant Director for Program Planning and Evaluation. To my immediate right is Dr. Richard Krause, whom you know, our Senior Scientific Advisor.

You know Dr. Raub and Mr. Williams, of course.

Mr. NATCHER. We are delighted to have all of you back before the committee. This especially applies to you, Dr. Krause. Nice to have you back.

Now, Dr. Schambra, we will be pleased to hear from you at this time.

Dr. SCHAMBRA. Thank you, Mr. Chairman.

If I may, Mr. Chairman, I would like to submit my complete statement for the record and make a brief opening statement.

Mr. Chairman and Members of the committee, from what you have heard from Dr. Raub and my fellow Directors during the past week, I am sure you could not fail to catch the excitement about the progress being made against a host of diseases and health problems. For the Fogarty Center, this excitement takes on an added dimension as we welcome the changes in Eastern Europe and Latin America and explore opportunities to increase cooperation with these scientists.

The Fogarty Center's programs to promote cooperation between American and Eastern European and Soviet scientists are burgeoning with new applicants. Now that the Iron Curtain has parted and the Cold War has ended, it is marvelous to see the eagerness of researchers who want to work together against the common enemy of disease.

Mr. Chairman, even without the events in Eastern Europe, the role of international cooperation in biomedical research has never been more important. An elegant example of this is the recent discovery of the cystic fibrosis gene highlighted in Dr. Raub's opening remarks and mentioned by other Directors, and by Dr. Watson just a few minutes ago. This discovery was the result of cooperation between American and Canadian scientists. Although this research was funded by several NIH institutes, the Fogarty Center had an important role in making the arrangements with the Department of State to award a foreign research grant, in this case to Dr. Lap-Chee Tsui, a Canadian. This is only one example from several hundred I could cite to illustrate the participation of the Fogarty Center in international biomedical research.

This past year has been exceptionally productive for the Fogarty Center as we have completed the first full year of our International AIDS Epidemiology and Research Training Grants. We are currently training 140 scientists and health professionals from 11 African, 7 Latin American, and 8 Asian countries, and we conducted 25 in-country courses for over 1,000 junior health care personnel, nurses, and technicians. These trained individuals will be the front-line soldiers in our war on AIDS in these countries. We must strike at this disease wherever it exists if we are to contain it.

We have enlisted our Scholars-in-Residence in the global effort against AIDS. Mr. Chairman, if I may, I would like to introduce Dr. Olufemi Williams from Nigeria, our first scholar from Africa. Dr. Williams is working with NIH scientists on studies of the differences between the African and American forms of AIDS. We are very pleased to have him with us.

During the past year our fellowship programs for junior foreign investigators and mid-career U.S. researchers supported 128 scientists from 36 countries worldwide. Among their achievements is a new diagnostic blood test for the highly infectious dengue fever which occurs in epidemic proportions in the Caribbean and other tropical regions, and threatens the United States.

We are centrally involved in NIH's participation in 73 formal research agreements with 39 countries and multilateral organizations. Last year we negotiated new technology agreements with Bulgaria and Hungary. And we assisted the Japanese government to develop its Human Frontiers Science Program, a new source of research funds for American investigators in the fields of brain research and cell biology. We also launched a Latin American Initiative to stimulate increased cooperation between U.S. and Latin American scientists and to provide more training opportunities for junior Latin American scientists in the United States.

Mr. Chairman, it has been a productive and exciting year. We are looking forward to fiscal year 1991 for which our budget request is $16,355,000.

Mr. Chairman, I would be pleased to answer any questions you, or the Members of your committee, may have.

Mr. NATCHER. Thank you very much, Dr. Schambra.

[The information follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
John E. Fogarty International Center for
Advanced Study in the Health Sciences

The benefits from international cooperation in scientific research stretch back to the origins of modern medicine. They illustrate how much is gained whenever men and women of different cultures and viewpoints congregate.

In the 17th century, for instance, the young English physician William Harvey traveled to Italy's University of Padua, then the world's leading medical research center. There, Harvey studied with the great Italian anatomist Fabricius, who believed blood flows in and out of the heart like the ebb and flow of the tides. Their collaboration incited Harvey, on his return to England, to devise a series of inventive experiments to see if Fabricius was correct. Contrary to Fabricius' views, Harvey found that the heart pumps the blood to circulate throughout the body--a key discovery in the history of medicine. This turning point hinged on two researchers from two nations working together in one laboratory.

As biomedical scientists face the 21st century, such international collaboration is more vital than ever for achieving the advances necessary to improve the health of people worldwide. It is the mission of the Fogarty International Center (FIC) for Advanced Study in the Health Sciences to facilitate such collaboration. For over 20 years, FIC, the international arm of the National Institutes of Health (NIH), has worked to promote worldwide collaboration on many levels--scientist-to-scientist, institute-to-institute, and nation-to-nation.

FIC accomplishes this goal in part through a variety of fellowship and exchange programs that support scientists at every career stage and bring about the kind of dramatic advances made possible by Harvey's sojourn in Italy. I would like to briefly illustrate some of these programs and their rewards.

Our International Research Fellowship (IRF) program brings junior foreign investigators to work in U.S. laboratories. It has supported more than 2,700 scientists from more than 50 developed and developing countries since 1958. In the last fiscal year (FY) alone, FIC funded 90 IRF awards to investigators from 35 countries. Their work has produced such gains as the following examples:

o A new diagnostic blood test for the viral disease dengue fever, a highly infectious illness that occurs in epidemic proportions in the Caribbean and other tropical regions. The new test resulted from collaborative research by an IRF awardee from Thailand and scientists at the University of Massachusetts. Their test uses recombinant DNA technology to detect antibodies to dengue fever in a blood sample. The test is simple and reliable, and will help physicians diagnose the sometimes fatal disease in its early

stage. It also will enable epidemiologists to monitor future dengue outbreaks.

o Discovery of a biochemical abnormality in the brain that may play a role in epilepsy. An IRF from Italy, collaborating with scientists at the University of Maryland, found the brain mechanism for producing and releasing quinolinic acid, an amino acid important in transmitting nerve messages. The researchers believe that an abnormal concentration of quinolinic acid in the brain contributes to the development of epilepsy. If so, certain forms of epilepsy may be treatable by correcting the faulty brain mechanism.

The Senior International Fellowship (SIF) program supports more-established U.S. scientists to conduct research overseas with foreign colleagues. Since 1975, the SIF program has funded nearly 650 U.S. scientists; in FY 1989, it awarded fellowships to 38 U.S. investigators. Their studies are making such strides forward as the following:

o Discovery of mechanisms in the brain involved with memory storage. A University of Alabama SIF and scientists at the Australian National University investigated specialized structures that transmit messages as electrical impulses between nerves. Their work may lead to the development of ways to reduce the memory deficits caused by such progressive neurological disorders as Alzheimer's disease.

Finally, Fogarty's Scholars-in-Residence program brings internationally renowned U.S. and foreign scientists to the NIH, where they conduct advanced studies and interact with the Institutes' investigators. In the past fiscal year, these scholars published more than 60 scientific papers on such topics as calcium's role in muscle functions and cardiac failure, and genetic markers for coronary disease susceptibility. Their accomplishments include the following:

o Potential new types of vaccines based on immune-cell manipulation. A scholar from Sweden's University of Stockholm and investigators at the National Institute of Allergy and Infectious Diseases have identified which CD4 and CD8 immune system T cells react to the foreign chemicals or antigens produced by specific malaria parasites. These T cells stimulate the secretion of IL-2 lymphokine, a substance that increases immune system activity, intensifying the body's ability to destroy invading bacteria. The finding will help scientists choose antigens for use in effective malaria vaccines--and perhaps lead to T-cell immunity vaccines for other diseases.

Fogarty also has created special research and training fellowship programs as a response to the global AIDS epidemic, which has spread from its initial risk groups to women and children, particularly those in African and other developing countries. These programs are training much-needed epidemiologists from developing countries, so they can conduct research on the spread of AIDS and perform drug and vaccine clinical trials. In FY 1989, these programs supported 140 participants from 26 countries.

Fogarty's many international activities extend beyond its grant and fellowship support, however. The Center serves as the keystone in guiding Federal Government policymakers and coordinating the 73 formal agreements between the NIH and 39 countries and multilateral organizations, such as the World Health Organization. These efforts include administrating NIH participation in collaborative clinical drug trials and other studies, and fostering new initiatives for international cooperation. These efforts are crucial because of the speed with which new health menaces spread worldwide and the changing political conditions that can open or close doors to collaborative research.

For instance, Fogarty has moved quickly to take advantage of the changes occurring in Eastern Europe, where eased political constraints are creating new opportunities for scientific collaborations. Our efforts in FY 1989 included helping to negotiate a new science and technology agreement between the United States and Hungary. The agreement, proposed by President Bush, targets cooperative projects in medicine and the environment. It also establishes a joint fund to support collaborative scientific research.

Members of our staff also were part of a delegation to Moscow that successfully expanded the U.S.-U.S.S.R. Health Agreement to include NIH collaborations on the human immunodeficiency virus, which causes AIDS, and medical primatology, which deals with the use of primates in medical research.

Western Europe is undergoing dramatic changes, too, and Fogarty has been preparing policy papers for the White House Science Advisor on what the 1992 economic merger will mean for U.S. biomedical research.

Fogarty also has begun a "Latin American Initiative." The initiative's objectives are twofold: to facilitate cooperation in new research efforts, such as those on the human genome and neurological diseases; and to increase training opportunities for junior Latin American scientists.

I have time to mention only two other interesting activities. First, I have agreed to be the NIH coordinator for a Vatican-sponsored conference on the neurosciences, a field whose importance was underscored by congressional legislation making the 1990's the "Decade of the Brain." As coordinator, I will help develop and organize the participation of all of the Institutes.

Finally, our staff helped the Japanese Government and other Economic Summit countries plan and implement the new Human Frontier Science Program, which will support basic research on the brain and molecular biology.

The 1990's promise unprecedented opportunities for collaborative scientific projects. By taking advantage of these opportunities, we can improve the health of Americans and of people worldwide.

Our 1991 budget request is $16,355,000. Mr. Chairman, I am pleased to answer any questions you or your colleagues may have. Thank you.

CURRICULUM VITAE

Name: SCHAMBRA, Dr. PHILIP E.

Birthdate: November 8, 1934 - Saginaw, Michigan

Education:

1956 -	B.A., Rice University
1961 -	Ph.D., Yale University
1961-1963	Postdoctoral, Institut fuer Strahlenbiologie, Germany
1964-1966	Postdoctoral, University of California, Berkeley

Professional History:

1956-1958	Research Assistant, Biophysics Department, Yale University.
1958-1961	Predoctoral Fellow, National Cancer Institute, Biophysics Department, Yale University.
1961-1963	Research Associate, Institut fuer Strahlenbiologie, Karlsruhe, Germany.
1964-1965	Instructor, Department of Medical Physics, University of California, Berkeley.
1964-1967	Research Biophysicist, University of California, Berkeley.
1966	Laboratory Director, National Science Foundation Summer Institute in Radiobiology, University of California, Berkeley.
1967-1968	Grants Associate, National Institutes of Health.
1968-1971	Budget Examiner, Office of Management and Budget, Executive Office of the President.
1971-1974	Staff Member, Council on Environmental Quality, Executive Office of the President.
1974-1980	Associate Director for Interagency Programs, National Institute of Environmental Health Sciences, NIH.
1980-1984	Chief, International Coordination and Liaison Branch, Fogarty International Center, NIH.
1984-1988	Science Attache and PHS International Health Representative, U.S. Embassy, New Delhi, India.
1988-	Director, Fogarty International Center, National Institutes of Health

Honors and Awards:

1989	PHS Superior Service Award
1984	NIH Merit Award
1982-1989	Outstanding Performance Ratings
1986-1988	Merit Performance Awards
1987	Secretary DHHS Certificate of Appreciation
1964-1966	NASA Research Fellowship, University of California, Berkeley
1958-1961	National Cancer Institute Fellowship, Yale University

EASTERN EUROPE AND THE SOVIET UNION

Mr. NATCHER. Will recent events in the Soviet Union and Eastern Europe lead to more extensive exchanges between NIH and these countries?

Dr. SCHAMBRA. I hope that it will, and in fact, looking at our experience over the past year, we have already seen a substantial increase in participation with Soviet and Eastern European scientists in programs of the NIH and the Fogarty International Center.

Although we have had a number of programs with these countries for over 20 years, these have been at a relatively low level of participation because the influence of the political leadership in these countries constrained participation quite strongly.

As a result of recent developments in the countries of Eastern Europe and the Soviet Union, we are seeing a major increase in requests for participation in our programs, and we expect a continued and growing demand from those countries.

Mr. NATCHER. Is there any discussion at this time, Doctor, about increasing the Center's budget to deal with these opportunities and demands?

Dr. SCHAMBRA. When we perceived that this was going to be a permanent political change in the countries of Eastern Europe and the Soviet Union, staff of the Fogarty Center surveyed the interests which the other institutes of NIH have in their particular areas of research responsibility with these countries and, combined with FIC's own mechanisms—our fellowship and training programs—we developed a proposal which was circulated within the NIH and the Department. It has received a very positive reaction thus far both at the NIH and the Department.

That proposal consists of essentially five parts. The first part would be a new program of research grant supplements that would provide resources to American scientists already supported by the Institutes at NIH. This new money would allow them to develop scientific collaboration specifically with Soviet and Eastern European scientists.

We would also propose to expand our research fellowships—to support Eastern European scientists in U.S. laboratories for 1-2 years; and our training programs in AIDS—to provide training for health professionals and researchers from those countries to deal with a problem which is now recognized as being more serious than previously thought.

Additionally, we propose a program of short-term exchange visits between U..S and Eastern European scientists for the purpose of exchanging techniques and information and developing joint research projects.

The last program that we would propose would support conferences and workshops. This program would provide the funding for scientists to get together to develop the scientific strategies needed to deal with the severe problems they face in their countries, and from which we would also benefit.

Altogether, we have estimated that this five-year proposal would require approximately $4 million in the first year, and approximately $5 million in each of the second through fifth years.

I would be pleased to submit for the record further details on that proposal if you would like.

Mr. NATCHER. We would like to have you [illegible] that, Dr. Schambra.

[The information follows:]

EASTERN EUROPEAN INITIATIVE

The FIC has developed plans for a 5-year Eastern European Initiative that ranges in cost from $4 million for the first year to $5 million in each of the following years. The essential elements of the first year of this Initiative are:

Research grants for U.S. scientists to conduct collaborative research with Eastern European scientists. American scientists who already have research grant support from NIH (and therefore already have an active, funded domestic research program) will be invited to apply for these grants through the regular NIH grants review process. These grants will cover additional costs of conducting research in the American scientist's laboratory in cooperation with an Eastern European scientist. They will provide for the purchase of supplies and equipment needed by the Eastern European scientific collaborators in those instances where this would expedite the progress of the research. These grants would also pay for scientific exchanges so that the investigators in both countries can work together. Topics covered by these research grants would include cancer, cardiovascular disease, influenza and virus diseases, neurological disorders, environmental health, aging, and other scientific areas of high mutual priority.

Training grants in U.S. institutions for Eastern European scientists and health professionals who support these research efforts. These grants would focus on providing training for Eastern European scientists and health professionals concerned about scientific and medical aspects of AIDS. These grants could supplement existing international AIDS training grants already awarded by the Fogarty International Center to ten U.S. universities (Harvard, Cornell, Case Western Reserve, Emory, John Hopkins, Miami, Washington, Tulane, University of California at Berkeley, and the University of California, Los Angeles). These are active programs involving a large number of foreign students from many countries and would be able to receive additional trainees in a short period of time.

Research fellowships to support Eastern European scientists in U.S. biomedical research laboratories. These fellowships would be offered through the Fogarty International Center's International Research Fellowship Program which supports young scientists for one to two years to train and conduct research in U.S. biomedical research laboratories. These additional funds would enable FIC to respond to requests from Bulgaria and Czechoslovakia to participate in this program and to expand this program in our Eastern European countries. Training would be in any biomedical research area that was of mutual interest to a U.S. sponsor and the foreign fellow.

Short-term exchange research consultations between U.S. and Eastern European scientists. The support would be based on brief peer-reviewed applications from Eastern European and American scientists and would be for the purpose of supporting travel and per diem for scientists to develop collaborative research consultations in each others' countries for periods up to 6 months. The purpose of these consultations is to enable the scientists to develop plans for longer-term collaborations. The subject areas could include all fields of biomedical science of mutual interest.

Scientific workshops. Up to 10 workshops would be designed to bring together individuals with common scientific interests to exchange information, develop linkages and define areas of promising scientific collaboration between individuals and groups in both countries. The subject areas covered would be broad, but would include such topics as AIDS, human genome research, aging, environmental health, brain research, and cancer.

EUROPEAN COMMUNITY 1992

Mr. NATCHER. Doctor, what impact do you expect the 1992 European Community consolidation to have on U.S. research collaborations and on access to data?

Dr. SCHAMBRA. In our role as general advisor to the Director of NIH and the Institute Directors, we have been looking into this question. We examined what economic and political integration, in post-1992 Europe, would mean for the American scientific community and for international scientific cooperation.

It is clear that the purpose of the "European Communty 1992" is to achieve greater economic integration, to provide increased opportunities for scientists in those participating countries, and to collaborate with one another to provide additional funding for trans-European research projects. Our main concern has been to determine whether there was any inclination or tendency for this new Europe to freeze out American scientists from participating in collaborative research projects, whether there would be an increased problem in recruiting European scientists to the United States, or whether there would be an impact on the exchange of scientists between countries of Western Europe and the United States.

So far we have been reassured that the intentions of the countries participating in these developments are to maintain very strong links with the United States and to continue scientist exchanges, which we feel are absolutely necessary if, in fact, the scientific community on both sides of the Atlantic is to progress.

Mr. NATCHER. Mr. Conte, I yield to you.

Mr. CONTE. Thank you, Mr. Chairman.

Dr. Schambra, I join the Chairman in welcoming you before our committee.

With the new breeze blowing throughout Eastern Europe, you stand at the center of efforts to help those countries rebuild their biomedical research, and you have the background and experience to do the job right. We, on the committee, will see to it that you get the tools to do it.

Dr. SCHAMBRA. Thank you, sir.

NEUROLOGY RESEARCH

Mr. CONTE. As you know, the 1990s has been declared "The Decade of the Brain." What is your Center doing in the field of neurology research? What is the status of the International Neuroscience Fellowship Program and what have been some of the accomplishments of the Scholars who have participated? That is a mouthful.

Dr. SCHAMBRA. I am very pleased you asked that question, because I have some very interesting things to report.

Of course the Fogarty Center is a very small actor on the NIH stage in terms of its overall resources, the principal actor in neurology research being the National Institute of Neuorological Disorders and Stroke (NINDS). But over the years, we have been able to play a very important role not only through our own programs, but also in support of the NINDS.

I might cite a couple of examples from our International Research Fellowship Program. In one case, an International Research Fellow from Italy discovered the mechanism whereby quinolinic acid is produced in the brain, which in abnormal quantities could cause epilepsy.

One of our Fellows from Ireland developed techniques to develop radioactive tracers with monoclonal antibodies that can be used to seek out very small tumors in the brain.

One of our Senior International Fellows—this is a senior American scientist from Alabama whom we supported to go to Australia—is making discoveries on the structure of the brain which transmits nerve impulses. In turn, that information might shed some light on the cause of Alzheimer's Disease.

You asked about our Scholars-in-Residence Program. We currently have a Scholar in Residence from Sweden who is a world authority on brain research. He is working with scientists at the National Institute of Mental Health on the campus of the NIH to understand how electrical signals are transmitted in the brain.

As I mentioned in my opening remarks, we played a role in helping the Japanese government establish the new Human Frontier Science Program, which is funded for the most part by the Japanese. The headquarters will be in Strasbourg, France, and one of the two major areas of investigation is in brain research, the other in cellular biology. I expect that this new program will provide a considerable portion of its resources to support proposals from American scientists.

I mentioned our cooperation with the National Institute of Neurological Disorders and Stroke (NINDS) at the NIH, and that cooperation has been in the area of helping them award in recent years approximately 34 research grants to foreign scientists, as well as 27 research fellowship awards since 1977 under the International Neurosciences Fellowship program, which we co-sponsor with NINDS. We have also helped the NINDS negotiate special agreements with the Shanghai Brain Research Institute, and an institute in Italy to study the causes and treatment of stroke.

I could say more, but I think that is probably enough.

Mr. CONTE. I am happy to hear that because, you know, I am in favor of "The Decade of the Brain." We are bird-dogging it very closely, so I am very pleased to hear of all that activity.

I unfortunately will not be back here at 2:00 because of several meetings I have to go to. Therefore, I will miss you, but you will know I will be doing yeoman's work up there.

Thank you very much.

RESEARCH MANAGEMENT AND SUPPORT

Mr. NATCHER. Your request for research management and support is 9.6 percent above 1990. What is included in this increase besides three additional staff members?

Dr. SCHAMBRA. Mr. Chairman, our research management and support mechanism, in addition to salaries, supplies, and mandatory services costs, includes a number of distinctive scientific pro-

grams. Specifically, part of the increase will expand our existing exchange programs with Eastern Europe and the Soviet Union and fund new bilateral exchange agreements with these countries. It also includes a modest increase in funding for our Latin American Initiative.

INTERNATIONAL RESEARCH FELLOWSHIP PROGRAM

Mr. NATCHER. How do you plan to absorb the slight reduction in funding proposed for the International Research Fellowship Program in 1991?

Dr. SCHAMBRA. We plan to absorb the reduction by discontinuing short-term supplemental awards. We have found that over a number of years some of the Fellows, who had originally applied for a one year award, would realize that near the end of their fellowship they would need another month or two to complete a research project. We first require their U.S. hosts to endorse their requests for short-term extensions, and the FIC then reviews the requests for scientific merit and appropriateness. At the conclusion of this review and pending availability of funds, we would then provide short-term supplemental awards.

We will not be able to make those supplemental awards in fiscal year 1991.

Mr. NATCHER. What share of the international research fellowships awarded in 1991 will be two years in length and how does that compare to 1990?

Dr. SCHAMBRA. In FY 1991, we expect that about two thirds of the fellowships, or 60 awards, of the 90 initially made in FY 1990, will require second year funding. This amount is comparable to our plans for FY 1990 to support the second year funding of approximately 60 fellowships that were initially awarded in FY 1989.

Mr. NATCHER. Does the International Research Fellows budget request reflect the full two-year cost of the fellowships to be awarded in 1991?

Dr. SCHAMBRA. The 1991 budget request for the International Research Fellowships includes the second year funding for 60 noncompeting IRFs initially awarded in 1990, plus funding for 91 new competing awards.

Mr. NATCHER. What commitment base of funding for 1992 would your 1991 request produce?

Dr. SCHAMBRA. While a commitment base for 1992 has not yet been developed, we would expect to fund 60 noncompeting second-year awards initially funded in 1991, which would require a commitment of $1.6 million on the 1992 commitment base. We would also hope to be able to make 91 new awards, which would require approximately $2.5 million. These amounts assume no increase in stipend levels, however.

FELLOWSHIP STIPEND LEVELS

Mr. NATCHER. How do your stipend levels for international research fellows compared to those of other NIH research training programs?

Dr. SCHAMBRA. Mr. Chairman, our stipend levels under the IRF program currently average about $20,000 per individual, per fellow.

This is about $7,000 less than the average of equivalent type fellowships awarded by other components of NIH.

I might point out, by the way, that our fellowship stipend in this program has been unchanged since 1984.

Mr. NATCHER. Have you considered decreasing the number of fellowships offered in order to increase the stipend of those who are selected?

Mr. SCHAMBRA. We have, sir. It is a very hard choice to make, but based on the feedback that we get from the countries that we deal with, their assessment of the value of these fellowship programs, we feel that to reduce the number would not be satisfactory at all. Even though that would allow us to increase the stipend level, they would prefer us to keep the number up.

Mr. NATCHER. Dr. Schambra, we want to thank you and your associates for appearing before our committee at this time on behalf of your budget request for fiscal year 1991. It has been a good hearing.

Thank you very much.

The committee will recess for about five or 10 minutes.

[Recess.]

[The following questions were submitted to be answered for the record:]

Questions Submitted by the Subcommittee

INTERNATIONAL RESEARCH FELLOWSHIP PROGRAM

Mr. Natcher. How do the International Research Fellows (IRF) find their placements in the United States?

Dr. Schambra. International Research Fellows (IRF) are free to choose their own host, or sponsor, with whom they will conduct collaborative research and from whom they will receive advanced research training. As part of the application process, candidates make prior arrangements with a senior U.S. scientist who will serve as a sponsor, and who submits a complementary application. Initial contact with sponsors are made primarily through referrals from fellows' university faculty, Fogarty alumni, or nominating committee members. FIC staff also are asked to assist in locating appropriate U.S. universities that have strong programs in research areas in which the potential fellows are interested.

Mr. Natcher. What type of placements do the International Research Fellows obtain--how many are at NIH compared to universities or private industry?

Dr. Schambra. Throughout the history of the program, IRFs have consistently chosen sponsors at leading U.S. biomedical institutions. The top ten universities which predominantly serve as hosts to IRFs are: Harvard University; University of California, San Francisco; University of California, Los Angeles; Stanford University; Johns Hopkins University; Yale University; University of Washington; University of Wisconsin, Madison; University of California, San Diego; and University of Pennsylvania.

In FY 1988, only 7 of 92 awardees received their advanced research training at the NIH. In FY 1989, 3 of the 90 awardees came to the NIH; and in FY 1990, 5 of 80 awards made to date will go to fellows who plan to come to the NIH.

Mr. Natcher. How many countries currently submit applicants for International Research Fellowships?

Dr. Schambra. A total of 55 countries or regions have established nominating committees that function under FIC's guidelines and are eligible to participate in the program. In FY 1990, 38 nominating committees or about 70% submitted one or more applications.

Mr. Natcher. Do International Research Fellows count against NIH staffing ceilings if their assignments are on campus?

Dr. Schambra. No, fellowships do not count against NIH staffing ceilings.

Mr. Natcher. We have heard that the mix of developed versus developing countries participating in the International Research Fellowship Program is changing. What is the trend and how do you explain it?

Dr. Schambra. From 1980 to 1984, the participation rate of scientists from developing countries in the IRF Program averaged around 26 percent; while from 1985 to the present the average has increased to 33 percent. In this latter period, a number of nominating committees from developing countries joined the Program. For example, in 1982 both the People's Republic of China and countries in the Caribbean formed nominating committees; Bolivia and the Organization of African Unity (which includes all African countries that did not previously have nominating committees) joined in 1983; Ethiopia joined in 1985; and Costa Rica and the Regional Committee for South and Central America of the Pan American Federation of Associations of Medical Schools (which includes all South and Central American countries without nominating committees) joined in 1984.

While the addition of these nominating committees has resulted in more scientists from developing countries applying to this program, each applicant's proposal is reviewed for scientific merit by an NIH-chartered review group in competition with proposals from all other countries. Because awards are based on scientific merit and because FIC has no quota or target for funding of applicants from developing countries, the increase in the "success rate" of scientists from these countries reflects the fact that they have become more competitive.

FIC BUDGET TABLES

Mr. Natcher. Display the crosswalk summary on page 146 of the budget justification with the addition of columns for 1989 and 1990.

Dr. Schambra. Crosswalk summary tables for fiscal years 1989, 1990 and 1991 follow:

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

FY 1989 Actuals
CROSSWALK SUMMARY

(Dollars in thousands)

PROGRAM ACTIVITY:	Research Grants: Other Research	Research Management and Support	Total
International Research Activities:			
Extramural Programs:			
International Research Fellowships:	$2,959	---	$2,959
Competing	2,446	---	2,446
Noncompeting	0	---	0
Supplements	513	---	513
Senior International Fellowships	926	---	926
Scholars-in-Residence Awards	503	---	503
International Training Grants in AIDS Epidemiology	3,630	---	3,630
International Postdoctoral Research and Training Grants in AIDS	692	---	692
Subtotal, Extramural Programs	8,710	---	8,710
Research Management and Support:			
Intramural Activities:			
International Research Coordination and Scientist Exchanges	---	624	624
International Services and Communications	---	640	640
International Advanced Studies in the Health Sciences	---	435	435
Special International Activities	---	297	297
Subtotal, Intramural Activities	---	1,996	1,996
Program Management and Support	---	3,458	3,458
Subtotal, Research Management and Support	---	5,454	5,454
Total, FIC	8,710	5,454	14,164

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

FY 1990 Request
CROSSWALK SUMMARY

(Dollars in thousands)

PROGRAM ACTIVITY:	Research Grants: Other Research	Research Management and Support	Total
International Research Activities:			
Extramural Programs:			
International Research Fellowships:	$4,056	---	$4,056
Competing	2,457	---	2,457
Noncompeting	1,599	---	1,599
Supplements	0	---	0
Senior International Fellowships	952	---	952
Scholars-in-Residence Awards	600	---	600
International Training Grants in AIDS Epidemiology	3,649	---	3,649
International Postdoctoral Research and Training Grants in AIDS	700	---	700
Subtotal, Extramural Programs	9,957	---	9,957
Research Management and Support:			
Intramural Activities:			
International Research Coordination and Scientist Exchanges	---	815	815
International Services and Communications	---	656	656
International Advanced Studies in the Health Sciences	---	360	360
Special International Activities	---	549	549
Subtotal, Intramural Activities	---	2,380	2,380
Program Management and Support	---	3,319	3,319
Subtotal, Research Management and Support	---	5,699	5,699
Total, FIC	9,957	5,699	15,656

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

FY 1991 Estimate
CROSSWALK SUMMARY

(Dollars in thousands)

PROGRAM ACTIVITY:	Research Grants: Other Research	Research Management and Support	Total
International Research Activities:			
Extramural Programs:			
International Research Fellowships:	$4,011	---	$4,011
Competing	2,457	---	2,457
Noncompeting	1,554	---	1,554
Supplements	0	---	0
Senior International Fellowships	952	---	952
Scholars-in-Residence Awards	600	---	600
International Training Grants in AIDS Epidemiology	3,847	---	3,847
International Postdoctoral Research and Training Grants in AIDS	700	---	700
Subtotal, Extramural Programs	10,110	---	10,110
Research Management and Support:			
Intramural Activities:			
International Research Coordination and Scientist Exchanges	---	929	929
International Services and Communications	---	791	791
International Advanced Studies in the Health Sciences	---	724	724
Special International Activities	---	660	660
Subtotal, Intramural Activities	---	3,104	3,104
Program Management and Support	---	3,141	3,141
Subtotal, Research Management and Support	---	6,245	6,245
Total, FIC	10,110	6,245	16,355

– Mr. Natcher. Provide a table showing the number of competing versus noncompeting International Research Fellowships in 1989-91.

Dr. Schambra. The table below provides the information requested.

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Budget Mechanism
(Dollars in thousands)

	1989 Actual		1990 Estimate		1991 Request	
PROGRAM ACTIVITY	No.	Amount	No.	Amount	No.	Amount
International Research Activities:						
International Research Fellowships:						
Competing	90	$2,446	91	$2,457	91	$2,457
Noncompeting	--	---	60	1,599	60	1,554
Supplements	--	513	--	---	--	---
Total	90	2,959	151	4,056	151	4,011

EASTERN EUROPE/U.S.S.R.

Mr. Conte. I'd like to follow up on what the Chairman said on Eastern Europe. The changed climate in Eastern Europe and the U.S.S.R. presents a unique opportunity to NIH and the Fogarty International Center to greatly expand our scientific exchange programs with those countries. What, in your opinion, are the health benefits for the people of both countries that would be achieved through scientific collaboration?

Dr. Schambra. Increased scientific collaboration would benefit both Americans and the people of Eastern Europe and the Soviet Union. In one respect, Eastern Europe offers unusual research opportunities of direct relevance to the United States because those populations are more homogeneous than that of the United States which has varied ethnic origins and disease patterns. The foreign populations can serve as control groups in research studies to compare to findings from U.S. subjects. Comparative international research can reveal much about disease etiology, treatment and prevention. For example, while mortality from cardiovascular disease has declined by 35 percent in American males between 1970 and 1982, it rose by 60 percent in Poland. Hungary has the highest rates of cardiovascular disease in middle aged men and women in the world. Hungary and Poland have the first and second highest rates of chronic obstructive pulmonary disease in the world. Perhaps linked to these disease rates are some of the worst environmental pollution problems in the world. A long-term lack of concern about the health effects of toxins, heavy metals and other dangerous substances has created unique research opportunities in Eastern Europe and, as these countries begin to identify and reduce health risks, collaborative research can help lead to improved life expectancy and decreases in morbidity.

Several opportunities are of particular interest because we believe collaborative medical research can improve the quality of life for Eastern Europeans by strengthening long-neglected medical research institutes and scientific communities. Strong western-oriented institutions and improved health are clearly beneficial to long-term European stability.

In addition to cardiopulmonary disease and environmental health, joint research could lead to progress on research targeting Lyme disease, osteoporosis and nutrition, child health and cancer. Americans and Eastern Europeans obviously have a strong common interest in combating the spread of AIDS. FIC's programs to train scientists, clinicians, and other health personnel from developing countries in different aspects of AIDS control and epidemiological research could be of very great benefit to Eastern European countries and the Soviet Union. The knowledge we have gained about AIDS will assist them in combating the threat at an early stage and perhaps prevent a widespread epidemic.

Ultimately, U.S.-Eastern European and Soviet collaboration can bring about important long-term scientific, technical, and commercial linkages. We would benefit from this collaboration by being fully informed about the advances in Eastern Europe and the Soviet Union in virology, vaccine development, genetics, and neurosciences.

Mr. Conte. What additional funding support would be needed to take advantage of this opportunity?

Dr. Schambra. FIC has developed a proposal for a 5-year Initiative to respond to the potential for U.S.-Eastern European and Soviet cooperation. The Initiative would help train scientists and develop linkages between institutions to form the basis of long-term productive joint research with U.S. biomedical researchers. The Initiative would utilize FIC's existing research and research training mechanisms so that its implementation can proceed rapidly should funds become available. The estimated cost of this Initiative ranges from $4 million in its first year, to $5 million in each of the 2nd through 5th years.

These resources would allow FIC to invite all the Eastern European countries and the Soviet Union to participate in the International Research Fellowship Program and the Scientist Exchange Programs. It will also enable considerable research cooperation and training in AIDS, including clinical trials of new drugs and vaccines for the prevention and treatment of AIDS. It would permit as well the NIH Institutes to undertake a broad range of disease-specific collaborative scientific research with centers of excellence in the region.

LATIN AMERICA

Mr. Conte. What special efforts is the FIC making to increase cooperation with Latin American Scientists?

Dr. Schambra. The FIC has developed a Latin American Initiative (LAI) in response to: Congressional, Departmental, and Administration interest in increasing U.S.-Latin American cooperation in science and technology; recommendations by the FIC Advisory Board that the FIC should be more active in promoting cooperation with developing countries; and the interests of U.S., Latin American, and Caribbean scientists to cooperate in biomedical and behavioral research in areas of mutual benefit.

The goals of the LAI are to: increase U.S.-Latin American scientific collaboration; provide U.S. scientists with access to research opportunities in Latin America and the Caribbean; contribute to the development of the Latin American scientific community; and advance U.S. relations with Latin American countries.

Within the resources allocated to begin the Initiative, we have concentrated efforts on informing the Latin American and U.S. scientific communities of existing opportunities to support research cooperation. We are also providing some funds to enable NIH scientists to visit laboratories in Latin America and the Caribbean for the purpose of developing cooperative scientific projects. And we have worked out new means for NIH laboratories to receive Latin American and Caribbean scientists into their research programs.

This Initiative would allow the FIC to provide new mechanisms for U.S. and Latin American scientists to undertake collaborative research. In particular, the FIC has identified a number of promising research opportunities of mutual interest, including neurological research relevant to the Decade of the Brain,

(e.g., neurological and genetic diseases, and cellular and molecular biology of endocrine and neurological functions), maternal and child health (low-birth weight, human lactation, adolescent pregnancy), AIDS, parasitic diseases and their interaction with HIV infection, effects of high altitude physiology on pulmonary and cardiovascular function, and other reactions to environmental and demographic change.

Mr. Conte. What would be needed to fully fund this effort?

Dr. Schambra. We have begun the Latin American Initiative with approximately $50,000 in FY 1990 and are requesting $100,000 in FY 1991. However, a program that would take full advantage of the many mutual scientific interests and opportunities, would cost $2.2 million annually for:

- Fellowships for Latin American and Caribbean scientists to conduct research and receive research training in U.S. laboratories;
- Supplements to domestic grants to increase the ability of U.S. scientists to undertake cooperative research activities with Latin American scientists;
- Short-term scientist exchanges by U.S. and Latin American scientists to engage in collaborative research and training; and
- Exploratory workshops to identify areas of mutual interest and to develop plans for future research cooperation.

AIDS

Mr. Conte. About one-third of the FIC budget is devoted to international AIDS activities. What have been some of your key accomplishments?

Dr. Schambra. The FIC has initiated two training programs that are specifically geared to training AIDS researchers world-wide and to preparing a cadre of epidemiologists in developing countries for clinical trials to test therapies and preventive strategies/vaccines for AIDS. Since 1988, the FIC has made 10 awards to U.S. institutions to train individuals from 11 African, 6 Latin American, and 5 Asian countries through its International Training in Epidemiology Related to AIDS Program. The accomplishments of this program include: degree training of 64 researchers in AIDS epidemiology; short-term training of 61 researchers in AIDS epidemiology for senior medical and other health personnel; and twenty-five short-term courses in laboratory and research techniques for 1,000 junior health care personnel, technicians and nurses.

In addition, under the International Postdoctoral Research and Training in AIDS Program the FIC awarded grants to 4 U.S. institutions in FY 1988. This program provides training of American and foreign scientists in research on the international aspects of AIDS and expects to provide advanced research training to about 20 persons each year. In the first year participants included 15

scientists from 2 African countries, 3 Latin American countries, and 4 Asian countries.

Mr. Conte. What efforts are you making with the other NIH AIDS programs and those of the World Health Organization?

Dr. Schambra. The FIC has sponsored and developed an International Network for AIDS Research and Training which facilitates communication among American AIDS researchers supported by FIC and other NIH institutes, the World Health Organization's Global Programme on AIDS, and others involved in international AIDS research and training. Two meetings of the Network were held in FY 1989, one at the NIH and the other in San Francisco.

The FIC also has represented the NIH at World Health Organization meetings on AIDS vaccine development in March 1989 and provided technical assistance to international organizations and foreign governments for research on vaccines and treatments for AIDS.

Mr. Conte. Can you tell us more about your work in Africa on AIDS?

Dr. Schambra. The FIC AIDS training programs are actively involved in Africa. Approximately 35 percent of the first year trainees under the epidemiology training program were from 11 countries in Africa and 2 African countries are represented in postdoctoral AIDS training program. The FIC also plans to support the V International Conference on AIDS and Associated Cancers in Africa scheduled to be held in October, 1990 in Zaire.

Also, Dr. A. Olufemi Williams from Nigeria, the first FIC Scholar-in-Residence from Africa, is currently at the NIH working on the spectrum of diseases produced by the AIDS virus in Africa, and is comparing them to the U.S. profile of AIDS-related diseases. He is also attempting to isolate and identify possible HIV variants in Africa that have the potential for spreading to other parts of the world.

Mr. Conte. Any research on the HIV-2 virus?

Dr. Schambra. Yes, there is research on the HIV-2 virus under FIC-funded awards, particularly with Dr. Max Essex who directs the Fogarty-supported AIDS training program at Harvard University's AIDS Institute. A Chinese postdoctoral trainee is conducting research with Dr. Essex on HIV-2 regulatory proteins and their use in seroepidemiological studies which should help to differentiate between HIV-1 and HIV-2 infection.

STIPEND LEVELS

Mr. Conte. Are FIC's stipend and award levels competitive enough to attract good scientists to its programs?

Dr. Schambra. We do receive applications from good scientists, although the low award levels increasingly influence the number of applications received, and the number of awards accepted. FIC's International Research Fellows currently receive stipends averaging $20,000 for 1 year, unchanged since 1984. In FY 1989, 10 percent of

the applicants who were awarded fellowships refused the award. One applicant, who was to do research at the NIH, stated he could not accept the award because the stipend was insufficient for him to support a family in the Washington, D.C. area. U.S. sponsors are constantly stating that the stipend is too low and imposes a hardship on awardees.

The Senior International Fellowship (SIF), awarded to mid-career U.S. scientists to conduct research in other countries, currently provides a stipend level of $15,000 per year and a foreign living allowance of $15,000. These levels are also unchanged since 1984. Comments made by former Senior International Fellows who participated in FIC's evaluation of the program as well as other scientists interested in applying to the SIF Program indicate that this award is insufficient to live abroad, particularly in Europe where most of the SIF awardees conduct advanced research. Clearly, we are losing good scientists who might consider applying to this important program. A major benefit of this program is that it gives U.S. scientists an opportunity to have direct access to European technology and to use this knowledge at their U.S. institutions.

The Scholars-in-Residence Program that brings world renowned scientists to the NIH to conduct advanced studies provides a $60,000 stipend which has not been raised since 1987. This level currently is too low to attract many of the world's top ranking scientists to spend a year at NIH.

Mr. Conte. What is the current stipend level?

Dr. Schambra. Under the International Research Fellowship Program, stipends average $20,000 a year; the Senior International Fellowship award is composed of a $15,000 per year stipend and a $15,000 living allowance; and the Scholars-in-Residence stipend level is $60,000. Each award includes additional amounts to cover travel to the research site and small amounts for research support.

Mr. Conte. Will you be able to increase stipends within this budget?

Dr. Schambra. No stipend increases are proposed in this budget request.

REFUGEE ASSISTANCE

Mr. Conte. Health of refugees and others who suffer from the plight of war and famine are of growing concern. Is there a greater need for more research and international cooperation for victims of natural disasters and war?

Dr. Schambra. Yes, there is a great need for more research and international cooperation in this area. One example of the NIH role in this area is the extensive research effort undertaken by the National Institute of Environmental Health Sciences through the National Toxicology Program on the health effects of methylisocyanate following the Bhopal disaster. Another example is the NIH role in studying the health effects of the Chernobyl nuclear accident, studies which will give scientists in both countries more insight into cancer and respiratory diseases which stem from over-exposure to

radiation. FIC provides support to the NIH institutes involved in these efforts.

Another example is FIC's response to the AIDS epidemic, a kind of "natural disaster." The FIC created two special AIDS training programs to develop a cadre of epidemiologists and other scientists from both developing and developed countries so the world may be better prepared to respond to the massive treatment and prevention of AIDS victims. Cooperation on HIV infection has also been added to bilateral agreements between the United States and USSR, Japan, Brazil, France, India, West Germany and Thailand.

The FIC has provided technical guidance to the DHHS Office of Refugee Health, and USAID's Office of US-Foreign Disaster Assistance, which have the primary organizational responsibility for responding to needs of victims of war, famine and other disasters.

NIH scientists conduct a number of collaborative programs in regions which have experienced a large influx of refugee populations, notably Somalia and Kenya, and many have remarked on the need for expanded cooperation in biomedical and other health research. Existing NIH programs could be beneficially extended to refugee health programs. For example, NIH conducts programs in India to correct severe nutritional deficiencies that lead to blindness and disabling and often lethal outcomes of measles infection. Through these studies, therapeutic advances have occurred in the use of Vitamin A supplementation in combination with oral rehydration. Another NIH research effort that should substantively benefit refugee populations involves research on measures which ensure perinatal health, including nutritional interventions and prophylaxis against infection.

Mr. Conte. What is the extent of your work in international development and assistance?

Dr. Schambra. The FIC's international AIDS training programs are increasing the expertise of developing world scientists in AIDS research and epidemiology. The programs are intended to enhance scientific manpower in developing countries and create an international epidemiological network that may help us to cope with emerging viruses. In addition, research programs undertaken with India and with Egypt in vaccine research and development have provided significant technology transfer in basic and applied microbiology, epidemiology and vaccine development which will have a wide and sustained application in developing nations and may lead to national self-reliance in vaccine production in some developing countries.

In the International Research Fellowship Program, one-third of the fellows in FY 1989 came from developing countries to conduct research and receive advanced research training in U.S. laboratories. After their fellowship in the United States of from 1 to 2 years, these fellows return to their home countries where they work on solving the health problems of their populations and continue collaborations with U.S. scientists.

FOREIGN DIGNITARIES

Mr. Conte. Who have been some of the major foreign dignitaries visiting your center in the past year?

Dr. Schambra. In FY 1989, the NIH had important visitors from every continent. To name a few, from Europe we were visited by His Royal Highness Prince Philippe of Belgium, a delegation of 3 members of the West German Parliament, Sir David Phillips, Chairman of the Advisory Board for the Research Councils of the United Kingdom, and V.I. Pokrovsky, President of the USSR Academy of Medical Science; from Latin America, Dr. Guillermo Soberon, Science Advisor to the President of Mexico and Executive President of the Mexican Foundation for Health; from the Middle East, Mr. Halil Sivgen, Minister of Health of Turkey, and Dr. Mohamed Ragheb Dewidar, Minister of Health of Egypt; from Africa, Dr. Fissena Meskal, General Manager of the Research Institute of Health of the Ethiopian Ministry of Health; from the Pacific, Dr. John Loy, First Assistant Secretary for Health of Australia; and from Asia, Han-Min Hsia, Chairman of the National Science Council of Taiwan, and Her Royal Highness Princess Chulabhorn of Thailand.

Mr. Conte. What activities did you plan for them?

Dr. Schambra. The FIC organizes visits for foreign dignitaries according to their areas of interest. Tours are given of the National Institutes of Health's centers of excellence frequently including laboratories, the National Library of Medicine and the Clinical Center. Meetings are scheduled to allow visitors time to discuss their interests--such as Human Genome research, cancer, cardiovascular, diabetes, neurological, or AIDS research--with Institute staff and to plan future collaborative activities.

NIH PASSPORTS

Mr. Conte. Doctor, I understand your Center will be assuming the responsibility for taking care of passports for all of NIH. Why is this change being made?

Dr. Schambra. We believe that providing passport and visa services for NIH international travelers is in keeping with the other services we provide in carrying out our international mission. We already serve as the focal point within the NIH for reviewing and approving foreign travel of NIH staff. We have excellent connections with the Department of State and foreign embassies which we use to expedite visas for international travel in conjunction with sudden emergencies, such as the Chernobyl incident, the earthquake in Armenia, and the chemical accident in Bhopal.

SCIENTISTS FROM DEVELOPING COUNTRIES

Mr. Stokes. To what extent are you able to bring scientists from developing nations to NIH through your fellowship and exchange programs? I understand that this year Fogarty has its first Scholar-in-Residence from Africa.

Dr. Schambra. Under the Scholars-in-Residence Program, the FIC does have its first Scholar-in-Residence from Africa this year. Dr. A. Olufemi Williams, from Nigeria, an outstanding researcher of the AIDS virus (HIV), is the Executive Secretary of the Organization of African Unity's Scientific Technical and Research Commission. His research is to define the spectrum of disease produced by HIV in Africa and compare their extent and severity with those that occur in the United States. Attempts are being made to isolate and identify possible variants of HIV in Africa that have the potential for spreading to other parts of the world. Other developing country Scholars-in-Residence came from Brazil, Chile, China, India, Mexico, and Peru.

Under FIC's International Research Fellowship Program that brings junior foreign scientists to the United States, 10 percent have conducted their research in NIH laboratories. In FY 1989, 31 percent of fellows in the program came from the following developing countries: Chile, China, Colombia, Guatemala, India, Mexico, Nigeria, Tanzania, Thailand, Uruguay, and Zimbabwe. Over the last ten years the participation of developing country fellows has increased from an average of 26 percent in the period 1980-1984 to an average of 33 percent in the period 1985-1989.

Mr. Stokes. Are you able to tell us about contributions made by these scientists after they return to their countries? What impact has this program had on research in developing nations?

Dr. Schambra. I can cite some examples. Under the Scholars-in-Residence Program, for instance, Dr. Jorge Eduardo Allende, Professor at the University of Chile has made significant contributions to development of science in his own country and worldwide. At the NIH, Dr. Allende wrote a Spanish language textbook in molecular biology while working in Dr. Marshall Nirenberg's laboratory at the National Heart, Lung, and Blood Institute. Since his return to Chile, in addition to continuing his research in the field of biochemistry, Dr. Allende has exerted a strong leadership role throughout the region as Coordinator of the Latin American Network of Biological Sciences (LANBIO). First established in 1985, LANBIO is a model for other regional networks, and is supported as part of the International Biosciences Networks by the International Council of Scientific Unions and the United Nations Educational, Scientific, and Cultural Organization (UNESCO). The success of this network has encouraged UNESCO to promote similar networks in Asia and Africa and among Arab countries.

A recent evaluation of the International Research Fellowship Program found that over 90 percent of the former Fellows returned to their home countries. Upon return, the majority of former IRFs assumed academic positions and conducted basic research in the biomedical and clinical sciences. As examples of contributions made by IRFs after their return to their home countries, a fellow from

India established the country's new center to analyze and classify mycobacteria of tuberculosis and leprosy. Another fellow from Brazil established new internationally-recognized linkages between pathology and immunology in schistosomiasis, Chagas disease, and leishmaniasis. In Nigeria, a former IRF conducted monoclonal antibody studies with African arena-viruses, Rift Valley fever vaccination studies, and plaque assays of lassa virus. A former IRF in Thailand is playing a leading role in promoting better scientific research methodologies, especially within the area of community health, as part of the WHO initiative, "Health for All by the Year 2000."

In a separate analysis, the FIC studied the impact that the scientific publications of former IRFs have on their respective countries' biomedical literature. It was found that former fellows in this program published in important internationally-recognized journals and contributed as much as 20 to 30 percent of the overall biomedical literature of their countries, particularly in Argentina, Brazil, Chile, India, and Mexico. This again demonstrates the significant impact the IRF Program has on science in developing countries.

AFRICAN COLLABORATION

Mr. Stokes. You mentioned a "Latin American Initiative" in your opening statement. Do you plan to undertake a similar initiative in Africa?

Dr. Schambra. During the current fiscal year, the staff of the FIC plans to actively seek other sources of support to begin a collaborative program between the NIH and African counterparts. The purpose of the collaboration will be manifold: to establish research associations that will lead to clinical research in AIDS and other communicable diseases of public health priority; to strengthen capabilities of African research centers through collaboration with the NIH; to initiate long-term collaborative ties; to share and ultimately transfer research findings in areas such as child health and infectious diseases; and to develop epidemiological surveillance skills to ensure that the growing international network of biomedical science includes centers of excellence in Africa. Given the natural history of recent epidemics like AIDS, it is essential that special attention be given to Africa in areas related to biomedical research. To assist in our efforts, we plan to approach USAID to develop cooperative plans for NIH-USAID collaboration in sub-Saharan Africa. Our goal is to match the scientific capabilities and objectives of the NIH with USAID programmatic and development goals.

AIDS COOPERATIVE PROJECTS IN EASTERN EUROPE

Mr. Stokes. In your opening remarks, you stated that the Fogarty Center has taken advantage of the changes in Eastern Europe. Will you be undertaking cooperative projects in Eastern Europe in the area of AIDS, in addition to the collaborative effort with the Soviet Union which you mentioned?

Dr. Schambra. Yes, we are actively working both with the Soviet Union and Eastern European countries on AIDS. As a result of the dramatic changes taking place in the Soviet Union and Eastern Europe, coupled with FIC's efforts to expand cooperation with biomedical

scientists in these countries, we have decided to authorize and encourage the directors of FIC-funded international AIDS training programs to include individuals from the Soviet Union and Eastern Europe. However, we have had to limit the amount of activity to no more than 10 percent of available funds in order to minimize the impact upon our commitment to developing countries in Africa, Latin America and the Far East/Western Pacific area.

In addition, the FIC is working with the NIH Office of AIDS Research to facilitate the participation of scientists from Eastern Europe and the Soviet Union at the VI International Conference on AIDS to be held this June in San Francisco.

Mr. Stokes. How much is requested for cooperative projects with Eastern Europe in the FY 1991 budget? How does it compare to FY 1990?

Dr. Schambra. In FY 1991 we plan to devote about $250,000 to support health scientist exchanges with Bulgaria, Hungary, Poland, Romania, and Yugoslavia, an increase of $50,000 over the amount planned for FY 1990.

NURSE RESEARCHERS

Mr. Stokes. Are nurse researchers participating in your programs?

Dr. Schambra. Nurse researchers are participating in FIC's research training programs, particularly the Senior International Fellowships and the international training programs in AIDS epidemiology.

AIDS COOPERATIVE PROJECTS IN EASTERN EUROPE

Mr. Dwyer. As you know, disease knows no boundaries. This is especially true of AIDS. With the fall of the government of Rumania and other communist regimes in Eastern Europe, the tragic story of Pediatric AIDS in those countries was brought into every American household. What cooperative efforts are underway with Eastern European public health ministries to apprise them of American progress in this area?

Dr. Schambra. A number of activities are either under way or planned to assure that ministries of health in Eastern European countries are well informed about U.S. progress in the fight against AIDS. In particular, we have sent communications to ministries of health in Eastern Europe and the Soviet Union inviting AIDS research scientists and technical specialists to attend the VI International Conference on AIDS to be held this June in San Francisco. We are prepared to support up to 28 people to attend this San Francisco conference. It is our hope that the contacts made in this way will lead to future collaborative research efforts. In addition, we are exploring ways to provide computerized databases to Eastern European and Soviet health ministries and scientists to allow them to access American AIDS-related literature and treatment protocols. Under FIC's proposed Eastern European Initiative, workshops, conferences, and other information exchange activities related to AIDS would be undertaken. Furthermore, extensive AIDS training efforts would be mounted through the existing FIC programs established to provide such training.

Mr. Dwyer. It is my understanding that in Eastern Europe, many children were infected with the AIDS virus because needles were not cleaned and sterilized before their use with the next child. What cooperative projects are underway to improve prevention programs in these countries?

Dr. Schambra. We are actively working with Eastern European countries on AIDS. As a result of the dramatic changes taking place in Eastern Europe, coupled with FIC's efforts to expand cooperation with biomedical scientists in these countries, we have decided to modify our international AIDS training programs to include scientists from Eastern Europe within the limited funds which are available for our overall AIDS training effort.

In addition, we are working closely with the National Institutes of Child Health and Human Development (NICHD) to determine if there is a constructive, mutual beneficial role for NIH to play in this situation. At present, we are awaiting a report from a pediatric AIDS expert supported by NICHD, Dr. Stephen Nicholas of the Babies Hospital of Columbia University, who has recently returned from Romania. We will develop our next steps after hearing from Dr. Nicholas.

The sooner we begin training Eastern European scientists, the sooner effective prevention programs can be implemented there. The FIC is also working with the NIH Office of AIDS Research to facilitate participation by scientists from Eastern Europe at the VI International Conference on AIDS.

Mr. Dwyer. Have Eastern European countries begun to use AZT, DDI, or any of the other experimental drugs used to combat AIDS?

Dr. Schambra. We are not aware that this has yet occurred to any significant degree, although the cooperative steps that the FIC has taken will greatly enhance the prospects that this will occur, and that these countries will be better able to manage their use.

OTHER COOPERATIVE PROJECTS IN EASTERN EUROPE

Mr. Dwyer. It is also my understanding that extreme air pollution coupled with an extraordinarily high rate of cigarette smoking has presented Eastern European countries with a tremendously high rate of lung and other cancers. What efforts are underway to bring American anti-smoking and other prevention programs to Eastern Europe?

Dr. Schambra. Both the National Cancer Institute and the National Heart, Lung, and Blood Institute have begun to be engaged in disease prevention collaborative activities with their Eastern European colleagues. While collaboration in prevention programs is in its early stages, we anticipate that this area will be of particular interest for activity within FIC's Eastern European Initiative. Several Eastern European countries have identified disease prevention and risk reduction as priority areas of concern and since the NIH has recognized expertise in these areas future FIC activities will take the Eastern European interests into account.

Mr. Dwyer. Are many Soviet and Eastern European scientists requesting fellowships to study American techniques to combat cancer?

Dr. Schambra. Over the past four years, 32 International Research Fellowship awards have been made to postdoctoral fellows from Hungary, Poland, and Yugoslavia to conduct collaborative research in U.S. institutions. Of these 32, three scientists have projects related to the study of techniques to combat cancer: two scientists from Hungary are studying leukemia cell proliferation and differentiation, and blood coagulation and cancer, respectively; and a scientist from Poland is studying the retinoblastoma-susceptibility gene in human cancers.

PSYCHIATRIC AND PSYCHOLOGICAL RESEARCH EXCHANGES

Mr. Dwyer. To what extent, if any, does the Fogarty Center promote exchanges and other programs in the area of psychiatric and psychological research?

Dr. Schambra. The Fogarty Center promotes and supports exchanges in all areas of relevance to the NIH and, through most of the exchange programs with Eastern Europe and the Soviet Union, also supports exchanges of relevance to other agencies of the Public Health Service including the National Institute of Mental Health. Behavioral research, including psychological and psychiatric is supported by FIC's fellowship programs to the extent that the activities relate to NIH's mission.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

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NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

For carrying out the activities at the John E. Fogarty International Center, [$15,556,000] *$16,355,000*.

(Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 1990)

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Amounts Available for Obligation 1/

	1989 Actual	1990 Appropriation	1991 Estimate
Appropriation	$16,074,000	$15,556,000	$16,355,000
Enacted administrative reduction	226,000	40,000	---
Subtotal, adjusted appropriation	15,848,000	15,516,000	16,355,000
Real transfer to: The Office of the Assistant Secretary for Health for AZT grants	-58,000	---	---
Comparative transfers to: The National Institute of Allergy and Infectious Diseases for the Gorgas Memorial Institute	-1,830,000	---	---
The Division of Research Resources for administrative costs of the RCMI program	-1,000	---	---
Comparative transfers from: The Office of the Director, NIH for FTE increase	+66,000	---	---
The Office of Research Services, NIH for passport activities	+139,000	+140,000	---
Subtotal, adjusted budget authority	14,164,000	15,656,000	16,355,000
Unobligated balance, lapsing	-51,000	---	---
Total, Obligations ..	14,113,000	15,656,000	16,355,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: FY 1989 - $530,000; FY 1990 - $1,539,000; FY 1991 - $1,587,000.

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Budget Mechanism

(Dollars in thousands)

	1989 Actual		1990 Appropriation		1991 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Grants:						
Other Research	154	$8,710	204	$9,957	204	$10,110
	FTEs		FTEs		FTEs	
Research Management and Support	61	5,454	64	5,699	67	6,245
Total		14,164		15,656		16,355
HIV/AIDS		(4,654)		(4,898)		(5,207)

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

CROSSWALK - 1989 Actual

(Dollars in thousands)

PROGRAM ACTIVITY:	Mechanism		
	Research Grants		
	Other Research	Research Management and Support	Total
International research activities ...	$8,710	---	$8,710
Research management and support	---	$5,454	5,454
Total	8,710	5,454	14,164

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

CROSSWALK - 1990 Appropriation

(Dollars in thousands)

	Mechanism		
	Research Grants		
	Other Research	Research Management and Support	Total
PROGRAM ACTIVITY:			
International research activities	$9,957	---	$9,957
Research management and support	---	$5,699	5,699
Total	9,957	5,699	15,656

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

CROSSWALK - 1991 Estimate

(Dollars in thousands)

PROGRAM ACTIVITY:	Mechanism		
	Research Grants		
	Other Research	Research Management and Support	Total
International research activities	$10,110	---	$10,110
Research management and support	---	$6,245	6,245
Total	10,110	6,245	16,355

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NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

FY 1991 Estimate
CROSSWALK SUMMARY

(Dollars in thousands)

PROGRAM ACTIVITY:	Research Grants: Other Research	Research Management and Support	Total
International Research Activities:			
Extramural Programs:			
International Research Fellowships:	$4,011	---	$4,011
Competing	2,457	---	2,457
Noncompeting	1,554	---	1,554
Senior International Fellowships	952	---	952
Scholars-in-Residence Awards	600	---	600
International Training Grants in AIDS Epidemiology	3,847	---	3,847
International Postdoctoral Research and Training Grants in AIDS	700	---	700
Subtotal, Extramural Programs	10,110	---	10,110
Research Management and Support:			
Intramural Activities:			
International Research Coordination and Scientist Exchanges	---	929	929
International Services and Communications	---	791	791
International Advanced Studies in the Health Sciences	---	724	724
Special International Activities	---	660	660
Subtotal, Intramural Activities	---	3,104	3,104
Program Management and Support	---	3,141	3,141
Subtotal, Research Management and Support	---	6,245	6,245
Total, FIC	10,110	6,245	16,355

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Summary of Changes

1990 Estimated budget authority	$15,656,000
1991 Estimated budget authority	16,355,000
Net change	+699,000

Changes:	1990 Current Estimate Base Pos. (FTEs)	1990 Current Estimate Base Budget Authority	Change from Base Pos. (FTEs)	Change from Base Budget Authority
A. Built-in:				
1. Within grade increase		$3,080,000		+23,000
2. Annualization of 1990 pay raise		3,080,000		+34,000
3. January 1991 pay raise		3,080,000		+84,000
4. One extra day of pay		3,080,000		+12,000
5. FTS rate increase		38,000		+1,000
6. Payment for centrally furnished services		800,000		+93,000
7. Service and supply fund increase		232,000		+59,000
8. Increased costs for supplies, materials, and other mandatory program expenses		1,819,000		+167,000
9. DHHS Working Capital Fund decrease		20,000		-1,000
Subtotal				+472,000
	No.	Amount	No.	Amount
B. Program:				
1. Other research	--	9,957,000	--	+153,000
	Pos. (FTEs)		Pos. (FTEs)	
2. Research management and support	64	5,699,000	+3	+74,000
Subtotal			+3	+227,000
Total change			+3	+699,000

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NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
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Budget Authority by Activity

(Dollars in thousands)

	1989 Actual		1990 Appropriation		1991 Estimate	
	FTEs	Amount	FTEs	Amount	FTEs	Amount
International Research Activities	--	$8,710	--	$9,957	--	$10,110
Research Management and Support	61	5,403	64	5,699	67	6,245
Subtotal, Obligations	61	14,113	64	15,656	67	16,355
Unobligated Balance Lapsing		51		---		---
Total, Budget Authority	61	14,164	64	15,656	67	16,355
HIV/AIDS	(3)	(4,654)	(3)	(4,898)	(3)	(5,207)

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
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Budget Authority by Object

	1990 Appropriation	1991 Estimate	Increase or Decrease
Total number of full-time permanent positions	59	59	---
Total compensable workyears:			
Full-time equivalent employment	64	67	+3
Full-time equivalent of overtime and holiday hours	1	1	---
Average ES Salary	$79,150	$81,920	+2,770
Average GM/GS grade	9.80	9.85	+.05
Average GM/GS salary	$35,432	$37,078	+1,646
Average salary, grades established by act of July 1, 1944 (42 USC 207).	$54,687	$56,601	+1,914
Average salary of ungraded positions	$1,350	$1,350	---
Personnel compensation:			
Full-time permanent	$2,192,000	$2,291,000	+$99,000
Other than full-time permanent	272,000	284,000	+12,000
Other personnel compensation	117,000	122,000	+5,000
Special personnel service payments	42,000	44,000	+2,000
Total personnel compensation	2,623,000	2,741,000	+118,000
Personnel benefits	457,000	477,000	+20,000
Benefits for former personnel	6,000	6,000	---
Travel and transportation of persons	70,000	73,000	+3,000

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	1990 Appropriation	1991 Estimate	Increase or Decrease
Transportation of things	17,000	18,000	+1,000
Rent, communications and utilities ...	181,000	189,000	+8,000
Printing and reproduction	69,000	72,000	+3,000
Other services:			
Centrally furnished services	800,000	881,000	+81,000
Other	1,299,000	1,604,000	+305,000
Supplies amd materials	65,000	68,000	+3,000
Equipment	112,000	116,000	+4,000
Grants, subsidies, and contributions..	9,957,000	10,110,000	+153,000
Total	15,656,000	16,355,000	+699,000

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Significant Items in Senate Appropriations Committee Report

Item	Action taken or to be taken
1990 Senate Report	
Nursing Research	
1. "The Committee is very pleased that the Fogarty International Center has made efforts to promote its research training and support programs to nursing institutions in the United States and abroad, and that it exhibits a continuing interest in receiving applications in the area of nursing research. The Committee urges the Center to continue these efforts, as well as to continue its efforts in developing appropriate links with the International Council of Nurses and other national and international nursing organizations in order to promote quality nursing research." (Senate Report No. 101-127, p. 157)	1. The FIC has given wide publicity to international fellowship programs in which postdoctoral nurse researchers may participate. Program posters have been distributed to all nursing school deans and department heads, and announcements have been placed in nursing journals and newsletters. Six fellowship awards have been given to support nursing-related research, including studies of the utilization of midwives in pre- and post-natal care, non-invasive approaches to handling urinary incontinence, self-regulation of hypertension, and decision-making in nursing. The FIC will continue to promote quality nursing research through its fellowship programs.

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
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Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1990 Amount Authorized	1990 Appropriation	1991 Amount Authorized	1991 Estimate
Research and Investigation	Section 301	42§287b	Indefinite	$15,656,000	Indefinite	$16,355,000
International Cooperation	Section 307	42§287b	Indefinite Such sums as necessary		Indefinite Authorizing legislation to be requested	
Total Budget Authority				$15,656,000		$16,355,000

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Appropriations History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1981	9,254,000	9,138,000	8,663,000	9,124,000
1982	8,438,000 2/	9,589,000	9,589,000	9,205,000
1983	10,147,000	10,147,000	10,147,000	10,147,000
1984	9,189,000	11,584,000	11,088,000	11,336,000
1985	11,426,000	11,526,000	11,929,000	11,679,000
1985 Proposed Rescission	- 241,000			
1986	11,464,000	11,529,000	11,606,000	11,551,000
1986 Sequester				- 497,000
1987	11,305,000	11,443,000	11,420,000	11,420,000
1988	11,166,000	12,128,000 3/	11,166,000	15,651,000
1989	11,338,000	16,074,000	16,474,000	15,848,000
1990	10,622,000 4/	15,579,000	15,532,000	15,516,000
1991	16,355,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.
2/ Reflects the September amendment; the original request was $9,589,000.
3/ Does not include funding for AIDS research. Consolidated at the Secretary's level.
4/ Does not include HIV-related funds, which were requested in a consolidated amount under the Office of the Assistant Secretary for Health.

Justification

John E. Fogarty International Center
for Advanced Study in the Health Sciences

	1990 Appropriation		1991 Estimate		Increase or Decrease	
	FTEs	BA	FTEs	BA	FTEs	BA
TOTAL....	64	$15,656,000	67	$16,355,000	+3	+$699,000
AIDS.....	(3)	(4,898,000)	(3)	(5,207,000)	--	+(309,000)

General Statement

The John E. Fogarty International Center (FIC) for Advanced Study in the Health Sciences is the NIH focal point for international cooperation in biomedical research. FIC's statutory mission is to: facilitate the assembly of scientists in biomedical, behavioral, and related fields; promote international scientific cooperation through its research programs, conferences and seminars; provide postdoctoral fellowships for foreign scientists to conduct research in the United States and for American scientists to conduct research in other countries; coordinate NIH international research activities; and serve as a focal point for foreign scientists and visitors at the NIH.

The global exchange of ideas is a key factor in the advancement of science. Diseases and their causes are unconstrained by national boundaries. Acquired immunodeficiency syndrome (AIDS), for example, has spread worldwide; meanwhile, heart disease has become an ever more common cause of illness in developing countries. Unless scientific information is shared on a scientist-to-scientist level, time, resources, and knowledge will not be wisely used to fight these diseases.

FIC confronts these and other challenges by supporting global cooperation in biomedical research. FIC's international research and training programs create opportunities for the vital exchange of ideas and data that produce scientific progress and so contribute to improved health worldwide.

The International Research and Awards Program supports American scientists to work abroad and makes it possible for foreign scientists to conduct collaborative research in U.S. laboratories. The International Advanced Studies Program brings eminent scientists from many countries to the NIH campus to conduct biomedical research, and to develop strategies for international health activities of benefit to the United States. The International Services and Communications Program provides management support and expert advice on the interpretation of immigration regulations to foreign scientists and guest researchers working in NIH intramural laboratories.

The International Research Coordination and Scientist Exchanges Program provides oversight for NIH's relationships with other countries and multilateral organizations, such as the World Health Organization, and supports the exchange of scientists under a number of formal agreements between the United States and foreign governments.

Overall Budget Policy

The FY 1991 budget request for the FIC is $16,355,000, providing an increase of $699,000 over the FY 1990 appropriation.

A total of $5,563,000 will be available in Other Research, reflecting a decrease of $45,000 from the FY 1990 Appropriation. The funding will provide for 189 FIC fellowships and Scholars-in-Residence awards, which is comparable to the number of awards estimated for FY 1990.

A total of $5,585,000 will be available in the FIC's Research Management and Support mechanism, reflecting an increase of $435,000 over FY 1990. The additional funding will be used to pay increased administrative costs and to provide for increased activity in several major program activities.

The FY 1991 budget request for the FIC includes $5,207,000 for AIDS research programs. This amount provides an increase of $309,000 over the FY 1990 appropriation.

Program Accomplishments

FIC's International Research and Awards Program supports American scientists working abroad and foreign scientists conducting cooperative research in United States laboratories. These awards are not limited to research on specific diseases but, rather, support basic and applied research in virtually every biomedical discipline.

Since 1958, FIC's International Research Fellowships (IRF) have been awarded to more than 2,700 scientists from over 50 developed and developing countries. In FY 1989, FIC funded 90 IRF awards to applicants from 35 countries to conduct collaborative research in U.S. laboratories in 27 states. Recent research accomplishments by IRFs include the following:

o Using recombinant DNA procedures, an IRF from Thailand and researchers at the University of Massachusetts developed a highly specific method for the early detection of the dengue virus. Dengue is a viral disease that occurs epidemically and sporadically in the subtropics and tropics, including the Caribbean basin. This simple, reliable technique will have broad applicability in the clinical diagnosis and epidemiological surveillance of this disease.

o An IRF from Italy collaborated with researchers at the University of Maryland on the biosynthesis of quinolinic acid, an amino acid believed to play an important role in the pathogenesis of epilepsy. They elucidated the mechanism whereby quinolinic acid is produced and released in the brain, and identified factors that regulate its concentration in nervous system tissue. These findings could provide a rational basis for developing a more effective treatment for epilepsy.

o An IRF from Brazil collaborated with neurobiologists at the Johns Hopkins University to determine the influence of various neuromodulators (particularly the nucleic acid derivative adenosine) on the embryonic development of the nervous system. The results of these studies increase our understanding of the various factors that control brain development very early in life and the neuromodulators which, if present in abnormal amounts, may be responsible for fetal brain malformations.

The Senior International Fellowship (SIF) is an FIC award that provides opportunities for American scientists to conduct cooperative research in foreign laboratories. Since 1975, 644 Fogarty SIFs have conducted collaborative research activities in 40 countries and, in FY 1989, 38 SIFs went abroad to continue this international research tradition. The following research examples illustrate the scientific merit of the program:

o An SIF from the University of Alabama conducted studies at the Australian National University on the specialized structures of nerve synapses (nerve-to-nerve connections) that transmit electrical impulses. The work has

direct relevance to our comprehension of mechanisms involved in memory storage and to the eventual development of strategies to reduce memory deficits characteristic of Alzheimer's disease.

In addition to supporting its own international research fellowship programs, FIC administers 10 foreign-sponsored programs that enable junior American postdoctoral scientists to conduct collaborative research in laboratories abroad. During the past year, 14 awards were made to U.S. scientists conducting research in neurobiology, molecular biology, physiology, immunology, and biomedical engineering in Finland, the Federal Republic of Germany, Israel, Japan, Norway, Sweden, Switzerland, and Taiwan.

The International Advanced Studies Program supports major areas of biomedical research through its Scholars-in-Residence and International Studies Programs.

Under FIC's Scholars-in-Residence Program, internationally distinguished scientists are invited to the NIH to interact with the NIH scientific community and to conduct advanced studies in contemporary biomedicine and international health. In FY 1989, FIC Scholars published 61 scientific papers in a variety of fields, including the neurochemistry of memory and learning, the role of calcium in muscle function and cardiac failure, antibiotic synthesis, genetic markers of coronary disease susceptibility, the structure and function of inner ear sensory receptors, and ethics and human genetics. In addition to their research and writing, FIC scholars who were at the NIH in FY 1989 were involved in international collaborative efforts that included such topics as intercellular communication in growth and development, control of the thyroid gland, and structure-function relationships in proteins. Examples of Scholar's research accomplishments are:

o Using a mouse malaria model, a Fogarty Scholar from Sweden and scientists at the National Institute of Allergy and Infectious Diseases clarified the basic mechanisms whereby immune cells (CD4 and CD8 T cells) confer protection against malaria parasites. The development of immunity was found to be associated with the stimulation and proliferation of antigen-specific T cells and the secretion of IL-2 lymphokine. Since antigenic components of malaria parasites vary greatly in their ability to induce protective immunity, this information will be of considerable value in selecting antigens for incorporation in malaria vaccines.

o A Scholar from Italy and an NIH colleague made important advances in determining the physicochemical structure of the special channels or pores of the cell membrane through which sodium flows. The direction of flow of sodium in these channels plays a major role in the transmission of signals (nerve impulses) in the nervous system. The Scholar has found that "masonry" lining the walls of the channels consists of chemical building blocks, composed of a single polypeptide containing four repeats, each of which has six transmembrane alpha helices. Discovery of such intricate chemical detail has revealed the molecular mechanism used by the channels to control the flow of sodium and therefore the propagation of electrical impulses in the nervous system. Efforts can now be directed to the discovery of abnormalities in the

function of channels and the consequent disturbances in nerve impulses in nervous system diseases. The ultimate goal is to develop chemical therapies to correct these defects.

o A Scholar from Japan succeeded in synthesizing nisin, an antibiotic derived from lactic acid streptococci. This has an inhibitory effect on gram-positive bacteria which cause strep throat and hospital-acquired wound infections. The ability to synthesize nisin is likely to make it less costly to produce and thereby increase its use.

o A Scholar from Switzerland defined basic mechanisms whereby intracellular calcium regulates a wide variety of physiological functions including muscle contraction, the electrical activity of cells, and intermediary metabolism. Such knowledge of the biological effects of calcium has broad applicability in medicine (e.g., in the development of more effective cardiovascular drugs and anesthetics or in the prevention and treatment of musculoskeletal diseases).

The International Studies Program has recently concentrated its efforts on hepatocellular carcinoma (liver cancer), particularly on vaccine development.

The occurrence of hepatitis B has been sharply reduced in the U.S. through the screening of blood to detect the hepatitis B virus (HBV) in blood donors as well as the administration of HBV vaccine to individuals who are in high risk occupations. But in many areas of the world, including Africa, Asia, and South America, HBV infection still occurs in epidemic proportions. Results of epidemiologic studies strongly suggest that early infection with HBV can lead to liver cancer (hepatocellular carcinoma) later in life. Thus, immunization with HBV vaccine might prevent this form of liver cancer. Indeed, if this is the case, the HBV vaccine would be the first "human cancer vaccine."

Epidemiologic research in regions of the world with a high incidence of hepatitis B, such as China, has revealed that newborn infants are highly susceptible to HBV infection through transmission from their infected mothers. Immunization after infection is unlikely to prevent hepatitis or liver cancer. It is anticipated that immunization of uninfected infants will prevent both HBV and the subsequent occurrence of liver cancer, but long-term follow-up studies will be needed to verify this possibility.

In view of these considerations, the FIC has joined with the National Cancer Institute (NCI) and the Chinese Academy of Medical Sciences (CAMS) to discuss the pathogenesis and prevention of liver cancer and to formulate strategies for identifying and treating HBV carriers who are at risk of developing liver cancer. This undertaking enhanced cooperative efforts already underway between NCI and CAMS to conduct long-term controlled studies to evaluate the HBV vaccine's efficacy against liver cancer development. Discussions on these issues took place concerning how best to implement the needed HBV vaccine studies in China and elsewhere in the world.

The International Services and Communications Program provides technical support to bring foreign scientists to the NIH to conduct collaborative research with NIH intramural scientists. Intramural scientists carry out one of the world's most comprehensive biomedical research efforts to discover the causes, preventions and treatments of both common and rare diseases. It is this scientist-to-scientist cross-fertilization that takes place in the laboratory that is critical to the success of the NIH in producing and disseminating the results of health research for the benefit of the United States and other nations of the world. Hence, international scientific cooperation should occur in NIH laboratories.

FIC programs that provide opportunities for foreign scientists to conduct cooperative research at the NIH include the NIH Visiting and Guest Researcher Programs, the Special Volunteers Program, and the Special Experts Program. FIC provides visa and immigration support for the scientists in these programs, and is charged with the analysis and evaluation of changing immigration regulations and their effects on NIH's international research cooperation. These programs provide for both research training of junior foreign scientists and opportunities for more senior foreign scientists to conduct collaborative research with NIH scientists.

During FY 1989, FIC arranged for the participation of 2,375 foreign scientists in laboratories of NIH institutes and in other PHS agencies located on the NIH campus. Foreign scientists constituted approximately one-third of the total number of researchers in NIH intramural laboratories and were contributors to a significant share of the scientific publications emanating from the NIH.

The International Research Coordination and Scientist Exchanges Program provides policy guidance, coordination, and general oversight for NIH participation in cooperative research agreements with other countries. It also links the NIH with other international components of the Department of Health and Human Services, the Department of State, Ministries of Health of foreign countries, and research institutions overseas. FIC currently administers NIH participation in 73 formal agreements with 39 countries.

Among these agreements are active scientist exchange programs with Austria, Bulgaria, France, Hungary, Poland, Romania, the USSR, and Yugoslavia. These programs, administered by the FIC, provide unusual opportunities for short-term research collaborations to U.S. and foreign scientists that can lead to more extensive, long-term joint research activities. During FY 1989, 24 U.S. scientists spent a total of 69 person-months in foreign laboratories and 38 foreign scientists spent 113 person-months working in U.S. laboratories as exchange scientists. Under the exchange programs with Austria and France, research collaborations have focused on such areas as molecular and developmental biology, genetics, pediatric surgery, and radiation effects on humans. Under the Eastern Europe and Soviet programs, activities have included research and research training in hormonal regulation of brain development, cystic fibrosis, nutrition, and molecular immunology and oncology, among many other biomedical subjects.

Changes in the political relationship between the United States and certain countries are providing greater opportunities for collaborative research in science and technology, including biomedicine. For example, the reforms occurring today in Eastern Europe provide unprecedented opportunities for American scientists to cooperate with their Eastern European colleagues. FIC's program staff have the skills and networks required to facilitate contacts that will enable biomedical research cooperation between the U.S. and these countries. During the past fiscal year, FIC staff strengthened international research relationships through the renewal of a number of successful agreements and the establishment of new linkages with scientists in Eastern Europe, as well as in Asia, Latin America, and the Middle East. FIC is also participating in new multi-country international efforts to provide increased opportunities for collaborative research. Recent progress has occurred through the following activities:

o As part of a U.S. delegation headed by the Assistant Secretary for Health, FIC participated in a meeting of the US-USSR Joint Health Committee in Moscow. At the session, two new areas of cooperation involving the NIH were added to the US-USSR Health Agreement--HIV infection and medical primatology. The Health Agreement was also amended to include language covering the protection of human subjects and laboratory animals. FIC is supporting greatly expanded exchanges between American and Soviet scientists under the Agreement.

o As part of a U.S. delegation to Hungary, FIC staff participated in negotiations for a new science and technology agreement between the two countries. The agreement, which was proposed by President Bush during a visit to Eastern Europe, identifies cooperation on the environment and medicine as two priority areas. It also establishes a joint fund with equal contributions from both countries to support collaborative research projects in several fields of science.

o FIC entered into discussions for renewal of the NIH-Bulgarian Medical Academy Memorandum of Understanding. This agreement establishes a successful scientist exchange program, which is leading to longer-term scientific cooperation between U.S. and Bulgarian scientists.

o FIC played a leading role in assisting the Japanese Government and other Economic Summit parties with the implementation of the Human Frontier Science Program. This program will support basic research on brain function and molecular biology to be carried out by scientists from the Economic Summit countries, including the United States.

o FIC staff were instrumental in the development of a new agreement between the NIH and Thailand. The program of cooperation will include research on AIDS, the use of natural products in biomedical applications, and cancer research. The cooperative efforts will also provide training opportunities for Thai physicians, and other health care professionals and scientists working on the AIDS problem.

o FIC played a key role in development of the US-Brazil Initiative in Science and Technology, established by former Presidents Reagan and President Sarney of Brazil. FIC staff participated in a technical meeting with the Brazilian National Council of Science and Technology to select projects for support under the Initiative's Biomedical and Health Research Area. Nine projects were selected for NIH-Brazil collaboration covering major infectious and parasitic diseases, cardiovascular diseases, and research in the neurosciences.

o FIC successfully negotiated a US-Egyptian program of cooperative research in biomedicine to be supported by USAID. The program will be funded with approximately $8 million over five years and will provide U.S. scientists with unique opportunities in such important public health priorities as emerging viruses, cancer, hypertension, and genetic-based diseases.

o The FIC represents the DHHS on an interagency task force established by the White House Science Advisor to assess the implications of European integration for U.S. science and technology interests. FIC staff are currently directing the preparation of a policy paper for the Science Advisor on the impact of these developments on U.S. human resource needs in science and technology. FIC staff have also developed policy documents for the NIH on European integration, and have begun to develop a plan to address the scientific challenges and opportunities an integrated Europe will present in the field of health research.

During FY 1989, plans were developed for a new initiative to facilitate biomedical research collaboration between U.S. and Latin American and Caribbean scientists. This Latin American initiative will provide opportunities for U.S. and Latin American scientists to develop cooperative activities relevant to NIH scientific priorities, and will increase research and research training opportunities for Latin American scientists.

FIC staff have also developed a plan for a program to support US-Eastern European biomedical research collaboration. This program would provide opportunities for collaborative research training grants, research fellowships, short-term exchange visits, and scientific workshops to explore mutual interests, develop linkages, and define areas of future scientific collaboration.

The global pattern of diseases threatening human well-being continually changes. FIC's programs weave tightly together to form a comprehensive yet flexible response to those health challenges. During FY 1989, these programs multiplied the number of qualified scientists worldwide, and enabled newfound discoveries to be discussed and studies to be undertaken in laboratories in remote areas of the world. Through continuing such combined and collaborative efforts the nature of these diseases can be understood and their incidence reduced.

AIDS Research Program

FIC AIDS Program

Because AIDS has spread so rapidly across international boundaries during the past decade, a cooperative multi-national effort is needed to stem this continuing global epidemic. For this reason, in FY 1989 the FIC continued an initiative to support international research training programs on AIDS. These programs are expanding the number of highly trained epidemiologists, postdoctoral scientists, and clinical investigators worldwide, who can increase research efforts in AIDS, especially in developing countries where AIDS is epidemic, and in the United States. The goal of this training effort is to develop an international cadre of scientists who can collaborate on research on the epidemiology and natural history of AIDS--wherever it occurs in the world--and on the conduct of clinical trials on new drugs and vaccines. To undergird these efforts, the FIC has developed a communication network to facilitate international AIDS research cooperation.

The FIC International Training Grants in Epidemiology Related to AIDS Program trains foreign scientists from developing countries in epidemiology. The training is designed to increase the scientists' capability for conducting epidemiological research related to AIDS in their home countries and for using epidemiology in prevention research and clinical trials of new drugs and vaccines. A total of 125 individuals from 22 developing countries began training under the first year of the epidemiology program. Of these, about 55% were from Latin America, 30% from Africa, and 15% from the Far East/Western Pacific area. In addition, 25 in-country courses were provided for over 1,000 students in 12 countries through the epidemiology training program.

The FIC International Postdoctoral Research and Training in AIDS Program provides opportunities for advanced postdoctoral research training for U.S. and foreign scientists. The training is in general at a more advanced level than that conducted through the epidemiology program. In addition this program provides training for a wider range of disciplines, including clinical and laboratory investigations of the natural history and pathogenesis of AIDS. Special attention is given to the theory and practice of the conduct of clinical trials for new drugs and vaccines. Under the postdoctoral program, training began for 15 individuals from 10 countries.

Recent Research Accomplishments

Both programs support research training in the U.S. and the investigators' home countries, and operate through FIC grants to U.S. institutions. Examples of research conducted through the FIC AIDS programs include the following:

o Research was conducted on the antigens of HIV-2 regulatory proteins and their use in seroepidemiological studies. The HIV-2 X protein was found to induce antibodies in some people and when present, indicates that the infection is due to HIV-2 and not HIV-1. Blood tests to detect these antibodies are now used to determine the nature of the infection in patients suspected of having AIDS.

o Research was done on the cell-mediated immune response to HTLV-1 and -2, and antigenic components of these viruses are now being identified. These components are used in immunologic research to determine antibody dependent cellular cytotoxicity and cytotoxic T-cell activity. These studies have revealed the importance of immunity in the pathogenesis of HTLV-1 and -2 infections. Such information provides the rationale for vaccine development.

o Research was done on the mechanism by which HIV kills infected T lymphocytes. These studies are concerned with the accumulation of DNA strand breaks in HIV-infected cells and the processes through which this accumulation leads to the activation of "programmed cell death." Such research may lead to new methods to reverse the infectious process.

o Research was carried out on the epidemiology of maternal-fetal transmission of HIV-1, including the role of breast feeding. This is being done through a community based study in Zambia that should serve as a prototype for similar investigations in other countries. Much more information is needed on this emerging aspect of the AIDS epidemic, which is moving into previously spared population segments.

o Research is under way on the clinical and laboratory features of Kaposi's sarcoma, a debilitating aspect of AIDS which occurs in some AIDS patients. This research will evaluate the efficacy of various chemotherapeutic agents in treating this complication.

o Research is being done to develop new tissue culture cell lines for the production of retroviral glycoproteins. Scientists have learned that the production of the glycoproteins is increased if the cells are coinfected with HIV and cytomegalovirus. This research may lead to new methods to prepare vaccines from the virus glycoproteins produced in infected cells.

o A Scholar from Nigeria, the first from Africa, is defining the spectrum of diseases produced by HIV viruses in Africa and comparing their extent and severity with those that occur in the U.S. where modes of transmission are different. Attempts are being made to isolate and identify possible variants of the HIV virus in Africa which have the potential for spreading to other parts of the world with a view to their early detection and control. A monograph is being prepared on the African perspectives of AIDS, which will be a valuable resource to American researchers.

FIC collaborated with the National Institute of Allergy and Infectious Diseases to establish an International Network for AIDS Research and Training. The network links the major international AIDS programs of the NIH, the Centers for Disease Control, the U.S. Agency for International Development,

the World Health Organization, the Global Program on AIDS, and the Pan American Health Organization. The network facilitates the coordination of research and research training needs and the formation of collective strategies to respond to emerging and unanticipated events as the AIDS epidemic progresses. Cooperation through the network also minimizes duplication of effort not only between the FIC and other NIH grantees, but also between U.S. and other governmental and international organizations.

Research Plans

The FIC will continue to support research on AIDS through its research and training programs, through support of the Third Pan American Congress on AIDS, and by continuing support of the International Network for AIDS Research and Training. Research will include epidemiology studies in the trainees' home countries to further strengthen their efforts in combatting their rapidly growing number of AIDS cases. Relations established between the U.S. and foreign investigators will also lead to long-term mutually beneficial research collaborations and will facilitate drug and vaccine intervention trials as these become feasible.

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International Research Activities

Authorization: Indefinite.

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$5,608,000	$5,563,000	-$45,000

Purpose and Method of Operation

The International Research Activities section provides funding for the FIC's extramural research programs. The extramural components include the International Research and Senior International Fellowships and the Scholars-in-Residence awards.

The International Research and Awards Program includes the FIC fellowships. The International Research Fellowship (IRF) provides funding for foreign scientists to conduct research in U.S. laboratories. The Senior International Fellowship (SIF) provides funding for senior U.S. scientists to conduct collaborative research abroad.

As part of the FIC's International Advanced Studies Program, the Fogarty Scholars are invited to the NIH to interact with the scientific community and to conduct studies of international interest and importance in contemporary biomedicine and international health. These well-established researchers, through laboratory research, lectures, seminars, publishing, or other mechanisms, contribute to the scientific and technological advances that improve health in the United States and abroad.

Rationale for the Budget Request

The 1991 budget request for International Research Activities is $5,563,000, which reflects a decrease of $45,000 from the 1990 appropriation. This amount will be used to fund 91 competing IRFs, approximately 60 noncompeting IRFs, 28 SIFs and 10 FIC Scholars, for a total of 189 FIC awards. This amount is comparable to the number of awards funded in FY 1990.

International Research and Senior International Fellowships and Scholars-in-Residence Awards

In FY 1991, the FIC will provide funding for International Research and Senior International Fellowships involved in multiple research areas. Specific topics will include research on neurotransmitters, cell and cancer biology, gene cloning and gene expression, and the epidemiology of infectious diseases.

During FY 1991, FIC Scholars will be involved in collaborative efforts including research on the: biomedical kinetics of muscle contraction; structural analyses and synthesis of biologically active compounds; epidemiology of aging; pathology and epidemiology of parasitic diseases; control of cerebral blood flow and the blood-brain barrier; role of the immune system in the pathogenesis of cancer; and electrolyte physiology and ion transport in tissues.

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Research Management and Support

Authorization: Indefinite.

Budget Authority:

1990 Appropriation		1991 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA
64	$5,150,000	67	$5,585,000	+3	+$435,000

Purpose and Method of Operation

FIC's Research Management and Support (RMS) area provides funding for a variety of program activities and administrative functions. General management and overall administrative expenses are included in this activity, as well as staff support. However, a significant portion of the RMS line item is devoted to the support of major program activities that include the International Advanced Studies Program, the International Research Coordination and Scientist Exchanges Program, the Public Health Services's Health Scientist Exchange Program, other bilateral exchanges, and international conferences.

Rationale for the Budget Request

The 1991 budget request for RMS is $5,585,000, providing an increase of $435,000 over the 1990 appropriation. In addition to covering the growth in built-in costs of TAPS and other increased program operations, major program costs to be covered in the RMS section include the following activities:

International Advanced Studies Program-During FY 1991, FIC Scholars will be conducting in-depth studies and analyses of the applications of molecular genetics to inherited nervous system disorders, new trends in peptide research, the fate of viral components in animal cells, membrane barriers in the control of cellular function, and DNA structure-function relationships.

FIC staff have been involved in preliminary planning efforts for international efforts to address the effects of global warming on health. Discussions will center on the effects of the spread of infectious diseases

into new areas of the globe due to changes in the earth's climate. Other topics involve the effect of ozone depletion on the skin's immunologic capacity to combat skin cancer as well as eye diseases.

International Research Coordination and Scientist Exchanges Program-Events in the Soviet Union and more recently in Eastern Europe have resulted in increased use of FIC's scientist exchange programs for research collaboration. In addition, these events present us with new opportunities and challenges in biomedicine that can contribute to the historic changes now taking place. FIC's current program activities make it possible for NIH to play a more active role in accommodating both the increased demand and new opportunities for increased research collaboration stimulated by these political changes.

FIC will continue efforts to improve North-South scientific collaboration with scientists of Central and South America, and the Caribbean. This effort, FIC's Latin American initiative, will improve and increase collaborative research efforts between U.S. and Latin American scientists to the benefit of both the U.S. and Latin American biomedical communities.

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NATIONAL INSTITUTES OF HEALTH

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Detail of Permanent Positions

	1989 Actual	1990 Appropriation	1991 Estimate
ES-4	1	1	1
GM/GS-15	9	9	9
GM/GS-14	5	6	6
GM/GS-13	5	4	5
GS-12	5	5	4
GS-11	3	3	3
GS-9	4	4	4
GS-8	0	1	1
GS-7	6	7	7
GS-6	6	7	8
GS-5	5	5	4
GS-4	6	3	4
GS-3	0	1	0
GS-2	1	0	0
Subtotal	56	56	56
Grades established by the Act of July 1, 1944 (41 U.S.C. 207):			
Director Grade	3	3	3
Total permanent positions	59	59	59

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Advisory and Assistance Services

Individual Experts and Consultants. The Fogarty International Center (FIC) utilizes the services of a tax consultant firm with the expertise necessary to provide information and guidance on federal and state tax laws applicable to foreign scientists working at the National Institutes of Health. Foreign nationals on fellowships or other assignments in the United States must satisfy certain U.S. tax obligations. Due to the many complex Internal Revenue Service regulations and revisions in the income tax laws affecting foreign nationals, it is difficult for FIC staff to adequately interpret these laws and regulations. In addition, income tax treaties between the United States and other countries are frequently modified or renegotiated, necessitating continual monitoring to assess how changes will affect the foreign scientists at NIH. NIH managers such as the Director, Division of Personnel Management and the Legal Advisor, NIH, concurred that outside expert advice to satisfy this important legal requirement is required. Funding for this activity was $50,000 in FY 1989, and is estimated to be $52,000 in FY 1990 and $55,000 in FY 1991.

In addition, the FIC procured the services of a consultant to advise the Director, FIC on the development of FIC programs and activities, especially activities in support of international efforts to combat AIDS. These services were provided only in FY 1989 at a cost of $16,000.

The FIC has a major programmatic interest in fostering international biomedical research and cooperation between U.S. scientists and scientists in developing countries. An important priority of this international research effort is the establishment of medical research laboratories in the developing countries, with one of the most successful efforts being the Biomedical Research Institute for Clinical Infectious Diseases (BRICID) in Cairo, Egypt. The FIC has contracted with the former director of the BRICID in order to identify issues pertaining to this successful effort in Egypt that would be applicable to establishing similar laboratories or research centers in other developing countries. A one-time cost of $10,000 is estimated in FY 1990 for this contract.

Costs in FY 1990 are estimated for the contracted services of a consultant to review what impact the European Community's (EC) policy on science and technology may have on U.S.-European biomedical collaboration. Of special concern is EC patent legislation which would influence science and technology agreements between the United States and European countries. This contract will commit $30,000 and begin in FY 1990, and will require an additional $30,000 and end in FY 1991.

Studies, Analyses, and Evaluations. Services of a firm were contracted at a one-time cost of $23,000 in FY 1989 to assess the scientific and professional accomplishments of former International Research Fellows. The expertise necessary to perform this service is not available within the FIC. The FIC's Office of Administration ensures the appropriateness of consultant services by reviewing and approving all requests for such services.

Management and Professional Support Services. The FIC performs a variety of activities to implement the administration and oversight of the NIH Visiting Program. Several of these activities, especially those relating to immigration matters and other legal concerns, are time critical, and an automated computer system linking FIC with other NIH components would facilitate data exchange, processing, and management. A commitment for a contract to develop an automated system for the NIH Visiting Program began in late FY 1989 at a cost of $14,000, and will continue in FY 1990 with a cost of $75,000 in that year.

Personnel Appointments. The FIC's Advisory Board is an on-going commitment to cover the functions and activities of the Board. The costs for these appointments were $5,000 in FY 1989 and are estimated at $6,000 in FY 1990.

TUESDAY, MARCH 20, 1990.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

WITNESSES

DR. DUANE ALEXANDER, DIRECTOR, NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

DR. WILLIAM F. RAUB, ACTING DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DR. HEINZ W. BERENDES, DIRECTOR, PREVENTION RESEARCH PROGRAM, NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

DR. FLORENCE P. HASELTINE, DIRECTOR, CENTER FOR POPULATION RESEARCH, NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

JOEL R. HEDETNIEMI, EXECUTIVE OFFICER, NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

ARTHUR D. FRIED, BUDGET OFFICER, NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. NATCHER. At this time we take up the budget request for fiscal year 1991 for the National Institute of Child Health and Human Development.

We have before the committee Dr. Alexander, the director.

Dr. Alexander, it is a pleasure to have you and your associates before the committee at this time. Before you give us your statement, tell us who you have with you there at the table.

Dr. ALEXANDER. Thank you, Mr. Natcher.

I would like to introduce first on my left Dr. Florence Haseltine, the director of our Center for Population Research; Mr. Arthur Fried, our budget officer; Mr. Joel Hedetniemi, our executive officer, and Dr. Heinz Berendes, the director of our Prevention Research Program.

Mr. NATCHER. We are delighted to have you all before the committee.

Now we would be pleased to hear from you, Dr. Alexander.

Dr. ALEXANDER. I have a full statement for the record. I will summarize it for you.

The research program of the National Institute of Child Health and Human Development (NICHD) cuts across age and disease categories and encompasses the study of normal, as well as abnormal, development.

The broad mission of the Institute and the relevance of its mission to some of the most critical public health problems of our time are reflected in the fact that NICHD research addresses eight of

the ten, 1992 Public Health Service priorities identified by the Assistant Secretary for Health.

These include infant mortality, AIDS, strengthening the family, drug and alcohol abuse, improving minority health, enhancing health promotion and disease prevention, environmental and occupational health, and maintaining research capacity.

INFANT MORTALITY

Reducing infant mortality is a long-standing national priority. The 1988 rate reached 9.9 deaths per 1000 live births, the lowest level ever recorded and a substantial reduction from the 1978 rate of 13.8, but still short of the 1990 objective of nine deaths per 1000.

Current data indicate that birth defects, SIDS, and low birth weight are the leading causes of death in infants. To reduce this nation's infant mortality rate, NICHD has placed a greater emphasis on research to elucidate their causes.

AIDS is an increasing problem among infants, children and women, and soon will become the fifth leading cause of death for children and young people from birth to 24 years of age. The NICHD AIDS research program focuses on preventing the transmission of the virus, treating the infection in infants and children, and understanding the biological activity of the virus.

NICHD and NIAID are combining the pediatric AIDS clinical trials network, thereby ensuring that the vast majority of HIV-infected children and pregnant women will have access to clinical trials and to state-of-the-art research and care.

The NICHD research program in contraceptive development addresses the problem of unintended pregnancy. The availability of safe, effective and acceptable methods of contraception is essential so that couples can better regulate their fertility.

Other NICHD research is directed at helping couples to have babies, by providing new approaches for overcoming infertility or reproductive diseases or disorders.

More than five million children under the age of three are now placed in some form of day care while their parents work. To address the many problems concerning the consequences of day care, the NICHD has launched a major cooperative clinical study of the emotional, social and intellectual development of children in varying child care settings.

Other families are faced with the additional challenge of care for a child with a physical handicap or mental retardation. The NICHD has initiated a special research program focused on the families of handicapped children, the way they function, and the effects of family environment on the children.

Many of the problems that I have mentioned, particularly infant mortality and teen pregnancy, affect minorities disproportionately. All of the research programs of the NICHD have the potential for improving minority health and some are targeted specifically to minorities.

Mr. Chairman, the NICHD fiscal year 1991 budget request favors basic research and totals $461,473,000.

I would be pleased to answer any questions you have.

[The information follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Institute of Child Health and Human Development

The research program of the National Institute of Child Health and Human Development (NICHD) cuts across age and disease categories and encompasses the study of normal, as well as abnormal, development. The broad mission of the Institute and the relevance of its mission to some of the most critical public health problems of our time are reflected in the fact that NICHD research addresses eight of the ten 1992 Public Health Service priorities recently identified by the Assistant Secretary for Health, Dr. James Mason.

These eight priorities include infant mortality, AIDS, strengthening the family, drug and alcohol abuse, improving minority health, enhancing health promotion and disease prevention, environmental and occupational health, and maintaining research capacity.

Reducing the infant mortality rate is a long-standing national priority. Not only is it one of the priority areas for 1992 identified by the Public Health Service, but reducing infant mortality was one of the primary health objectives for the nation established in 1980 in the Surgeon General's report Promoting Health/Preventing Disease.

The goal set for infant mortality in 1990 in that report was 9 deaths per 1,000 live births. The 1988 rate reached 9.9, the lowest level ever recorded and a substantial reduction from the 1978 rate of 13.8, but still short of the 1990 objective.

One objective that was met is a reduction in infant deaths in the area most amenable to technological intervention--neonatal mortality, defined as deaths occurring up to 28 days of age. Many of the technological advances that enabled a drop in this rate from 9.5 to 6.7 are attributable to NICHD research that has led to improvements in preventing birth trauma, providing nutrition, and treating gastrointestinal diseases, hypoxia, and respiratory distress syndrome.

However, other areas have shown little improvement over the past 10 years: there is still a broad gap between infant mortality rates for blacks and whites; there has been virtually no increase in the proportion of women receiving prenatal care early in pregnancy; there has been no reduction in the incidence of low birth weight and an increase in very low birth weight among blacks, a major factor in infant mortality; the proportion of babies born to unmarried women has increased; and AIDS--an infection not even identified 10 years ago--has emerged as a leading cause of death among infants and children.

The NICHD and the scientific community have worked hard over the past decade to achieve what progress has been made but it is obvious that the task is far from done. The Institute remains committed to the belief that research can help to overcome these and other problems. We enter a new decade armed with renewed determination and scientific advances to ensure that the PHS priorities for 1992 are addressed and the health goals set for the nation for the year 2000 are realized.

Current data indicate that birth defects are the leading cause of death in infants. To reduce this nation's infant mortality rate, a greater emphasis must be placed on research to elucidate the causes of these developmental defects. New technology allows investigations of developmental processes that never before have been explored. For example, several human birth defects now can be studied in animal models. NICHD has developed two mouse models for neural tube defects, one of the most common developmental defects of the central nervous system. Other scientists are testing a vaccine for cytomegalovirus, the leading cause in this country of congenital infections that damage infants, and studying the genes involved in hereditary immunodeficiency diseases.

An immunodeficiency disease that is acquired--AIDS--is an increasing problem among infants, children and women. Experts predict that during the 1990s AIDS will become the fifth leading cause of death for children and young people from birth to 24 years of age. The NICHD AIDS research program focuses on preventing the transmission of the virus, treating the infection in infants and children, and understanding the biological activity of the virus. A major laboratory study was completed recently to evaluate the suitability of using condoms, and condoms plus spermicides, in preventing the transmission of HIV. The results of this study show that the condoms on the American market are of high quality and should provide a substantial degree of protection from HIV and other sexually transmitted diseases in the general population. This and other studies have also demonstrated that spermicides used with condoms offer additional protection.

In ongoing research to develop better treatments for HIV infected infants and children, the NICHD is investigating the role of intravenous immunoglobulin in preventing bacterial infection in HIV positive children. The trial is being conducted in 30 hospitals around the country and has enrolled more than 330 children. This NICHD pediatric AIDS clinical trials network is joining forces with the pediatric AIDS network supported by the National Institute of Allergy and Infectious Diseases. By the union of the two networks, the vast majority of HIV-infected children and pregnant women will have access to clinical trials and to state-of-the-art research and care.

While AIDS is the newest and one of the most devastating diseases affecting family life in America today, other erosions are at work as well. More unmarried women, many of them

teenagers, are becoming mothers each year. Most of these pregnancies are unplanned and the young mothers are ill-equipped to deal with the demands of raising children. The adverse consequences of this premature childbearing are felt through subsequent generations. The NICHD research program in contraceptive development addresses the problem of unintended pregnancy. The availability of safe, effective and acceptable methods of contraception is essential so that couples can better regulate their fertility. NICHD-supported scientists are completing phase II clinical study of a polyvinyl sponge containing a spermicide. The study has shown that, overall, the sponge is as effective as the cervical cap or diaphragm, and is an attractive alternative to the consumer because of the ease of its use.

Clinical trials of two chemical analogs of a hormone produced in the brain that regulates reproductive processes are under way to ascertain the potential of these drugs for fertility regulation in men. If successful, these drugs could result in the first non-barrier, reversible contraceptive for men.

Other research is directed at helping couples to have babies. The NICHD supports a broad basic science program to provide new approaches for overcoming infertility or reproductive diseases or disorders. Scientists in one such study have discovered that nearly half of women with unexplained infertility produce antibodies to their partner's sperm. Finding this possible immunologic cause of infertility is the first step to restoring fertility to these women.

Even families with planned, wanted children have challenges to face. The "traditional" family with a father, who earns the family income and the mother who is a full-time homemaker, is far less prevalent than it used to be. More than five million children under the age of three are now placed in some form of day care while their parents work. To address the many questions concerning the consequences of day care, the NICHD has launched a major cooperative clinical study of the emotional, social, and intellectual development of children who have had varying child care experiences.

Other families are faced with the additional challenge of caring for a child with a physical handicap or mental retardation. The NICHD has initiated a special research program focused on the families of handicapped children, the way they function, and the effects of family environment on the children.

Some children, no matter how loving or responsible their parents, succumb to the temptations available in modern society. The NICHD conducts and supports research to expand our understanding of why some children, particularly adolescents, engage in risk-taking behavior leading to drug or alcohol abuse or to sexual behavior. Because women who abuse drugs often give birth to addicted infants, there is a particular need to support research on the effects of these drugs on fetal development.

Compounding the problem is the fact that many IV drug abusing women who become pregnant have infants with HIV infection.

The NICHD supports research to understand these risk-taking behaviors so strategies to prevent their occurrence can be designed. In one such study, investigators found that teenagers given a sexuality education program were no more or no less likely than adolescents not participating in the program to engage in sexual behavior. However, among those teenagers who were sexually active, those who had participated in the sexuality education program were much more likely to use contraception.

Many of these problems, ranging from infant mortality to teen pregnancy, affect minorities disproportionately. All of the research programs of the NICHD have the potential for improving minority health and some are targeted specifically to minorities. For example, in Baltimore, Maryland, an NICHD-supported project will utilize an intensive outreach program to bring women at high risk of poor pregnancy outcome into a comprehensive prenatal care system. By determining what approaches and which specific interventions work in this program, these can then be generalized to a larger population.

Underlying all of the research I have discussed today is a broad science base. The NICHD helps to maintain the Nation's research capacity through the support and conduct of research and research training. This year, an NICHD intramural scientist who first came to the Institute under a fellowship training program was awarded the prestigious Young Investigator Award by the Neuroscience Society for his work on glutamate receptors. Glutamate, a nerve signalling amino acid, probably holds the key to how the brain is damaged when deprived of oxygen and plays a role in fetal brain development and memory and thus in mental retardation. This award exemplifies the best at the NICHD and at the NIH--solid science combined with the development of new investigators. This is a tradition that we plan to maintain in the coming years.

Mr. Chairman, the National Institute of Child Health and Human Development FY 1991 budget request is $461,473,000. I would be pleased to answer any questions you have.

CURRICULUM VITAE

NAME	Duane Frederick Alexander, M.D.
BIRTH	August 11, 1940, Baltimore, Maryland
MARITAL STATUS	Married Marianne Ellis, Washington D.C., June 23, 1963; two children
EDUCATION	Pennsylvania State University, University Park, Pennsylvania, B.S. Degree, Pre-Medical, 1962 Johns Hopkins University School of Medicine, Baltimore, Maryland, M.D. Degree, 1966
INTERNSHIP	Intern and Fellow, Department of Pediatrics, Harriet Lane Service, Johns Hopkins Hospital, 1966-1967
RESIDENCY	Assistant Resident and Fellow, Department of Pediatrics, Harriet Lane Service, Johns Hopkins Hospital, 1967-1968
MILITARY SERVICE	1968-1970: Surgeon (LCDR), U.S. Public Health Service, and Clinical Associate, Children's Diagnostic and Study Branch, National Institute of Child Health and Human Development, (NICHD) National Institutes of Health (NIH) Bethesda, Maryland 1971-Present: From Surgeon to Medical Director, U.S. Public Health Service
FELLOWSHIP	Fellow in Pediatrics (Developmental Disabilities), John F. Kennedy Institute for Habilitation of the Mentally and Physically Handicapped Child, Johns Hopkins Hospital, 1970-71
LICENSURE	Maryland Board of Medical Examiners
CERTIFICATION	Diplomate, American Board of Pediatrics, 1973
POSITIONS HELD	
1971-74	Assistant to the Scientific Director, NICHD, NIH, Bethesda, Maryland
1974-78	Medical Officer (Staff), National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, DHEW
1978-82	Assistant to the Director, NICHD, NIH
1982-86	Deputy Director, NICHD, NIH
1986-present	Director, NICHD, NIH

CONTRACEPTIVE RESEARCH

Mr. NATCHER. Thank you, Dr. Alexander.

The National Academy of Sciences recently reported that private contraceptive research has come to a virtual halt in the United States. What measures are you considering to encourage drug companies to return to this area, Dr. Alexander?

Dr. ALEXANDER. We have worked with other government agencies, particularly the Agency for International Development, and with the drug industry in trying to encourage them to take over contraceptive products that we have developed.

The NICHD brings products through their earliest development and through phase 1 testing, sometimes phase 2, and tries to encourage industry to pick up the costs and the efforts required for phase 3 trials and marketing. We have had mixed success with this.

There is only one company in the United States at the present time, Ortho Pharmaceutical, still involved in active research on contraceptive development.

Unless we are able to do the initial work in our contraceptive development program, drug companies have not been willing under present circumstances to make the investment necessary to get to this stage.

We make every effort to encourage the private pharmaceutical industry to pick up the products that we have developed and tested that show some promise and effectiveness. One of the remaining hurdles, however, is the problem of product liability insurance coverage for the testing of those products, both for us and for the pharmaceutical industry, and for those products once they are on the market.

One of the recommendations from the National Academy of Sciences committee was to try and find some way around the problem of product liability insurance, perhaps by using FDA clearance of these products as adequate defense in possible product liability lawsuits for these companies.

RU-486 RESEARCH

Mr. NATCHER. How much money, Doctor, are you currently directing to research involving the drug RU-486 and for what purposes?

Dr. ALEXANDER. I will have to supply for the record the dollar amount that we are devoting to this. Most of that research at the present time is supported through our intramural program.

We are using RU-486 as a physiological probe to test the effect of absence of progesterone or blocking progesterone, as well as testing the anti-glucocorticoid properties of RU-486 in treating Cushing's Syndrome. We have demonstrated that the drug does work in patients with Cushing's Syndrome, and it has been lifesaving for some of those patients.

We have also been using it as a drug that may have effectiveness in treating some menstrual disorders, such as premenstrual syndrome, as well as possible contraceptive uses of this drug. We are not supporting any abortifacient research with RU-486.

[The information follows:]

RU 486

In FY 1989, the NICHD spent $960,000 on research involving the drug RU-486. This level of funding is expected to continue in FY 1990 and FY 1991.

AIDS RISK PREVALENCE SURVEYS

Mr. NATCHER. You have completed two projects, as you know, to pretest two studies of sexual behavior, one targeted to adolescents. Do you intend to go forward with either study using funds in your 1991 request or from elsewhere in the Public Health Service?

Dr. ALEXANDER. There are two projects, but neither is complete. The adult feasibility study—The National Survey of Health and AIDS Risk Prevalence (SHARP)—is funded through a contract. Funds for the feasibility study were provided in FY 1989. The feasibility study has been delayed and may require funds in FY 1991 to complete it. There are no funds in FY 1990 or FY 1991 for a full-scale study because such a study will not be contemplated until we have considered the feasibility study experience. The feasibility study is still under review at PHS by Dr. Mason, at the present time.

The American Teenage Study is to be funded under a grant. This grant is to be awarded to the University of North Carolina for a large national, population-based survey. This study would be conducted in two phases, first through participating schools and later in the home, with parental consent. The study would address knowledge and behavior regarding sexual activity as well as knowledge about AIDS. This project is ready for funding, but is under review in PHS and will probably not be acted upon until after a decision is made about the adult study. The funds for this grant will come from our regular research grant line over a five year period, hopefully beginning in FY 1990. Both of these studies are very important for our research program on behaviors related to AIDS risk and other adverse outcomes of sexual activity.

Mr. NATCHER. Dr. Alexander, is there any reason to believe the private sector could not support the cost of these studies?

Dr. ALEXANDER. It is highly unlikely that the private sector would do this. This is not the usual type of survey that the private sector does.

The magnitude of these surveys requires the participation of the Federal Government. The adult study represents a high degree of cooperation and joint funding by Federal agencies which need the type of data that would result. One example of that cooperation is that the sampling frame for the adult study is being provided from the National Center for Health Statistics.

It is also important to be able to indicate the significance and importance of these surveys to prospective respondents by stating that it is not a survey being done by some private organization or foundation, but has the endorsement and funding of the Federal Government. I think that adds to the credibility and will enhance the participation of subjects in these particular surveys.

MATERNAL AND PEDIATRIC AIDS

Mr. NATCHER. What is your best information, Doctor, regarding the percentage of infants of AIDS-infected mothers who are born

with AIDS antibodies? How many of these infants go on to develop AIDS themselves?

Dr. ALEXANDER. The best estimates from the studies that we have done are between 30 and 40 percent are infected. All of the infants carry passive antibodies from their HIV-infected mother, transferred across the placenta, so it is very difficult to identify at birth whether or not they are actually infected. By follow-up studies, which go on as long as a year and a half to two years, we are able to tell that about one third on the average of these infants actually are infected. We do not yet know how many of these will develop AIDS, but suspect that most will.

What is important is for us to be able to identify in the newborn period, from those infants who carry antibody from their mother passively, which ones are actually infected. This becomes increasingly important as treatment programs with antiviral drugs are developed because data from adult studies demonstrate that the sooner we can initiate those treatments, the better.

It is also important that we not treat unnecessarily the two thirds of infants who are uninfected. This is one of the reasons that the NICHD has put particular emphasis in its research programs on developing definitive diagnostic tests for use in the newborn.

We funded about $3 million worth of research in the past fiscal year to develop a new, definitive diagnostic test so that we can detect for sure that one third of infants who are infected and not risk treating unnecessarily the two thirds of infants who are not infected.

Mr. NATCHER. How many pediatric AIDS clinical trials are under way at this time, Doctor, and how many patients?

Dr. ALEXANDER. I can give you that information for the record. I don't have it right at hand. I will supply that for the record, Mr. Chairman.

[The information follows:]

PEDIATRIC AIDS CLINICAL TRIALS

The NIH is currently conducting 16 clinical trials for the study of a variety of therapeutic agents which may be useful in the treatment of HIV infection in children. In eight of these trials, a total of 564 children have been enrolled, and additional children are still being recruited. Eight other trials have had 232 children participating, and enrollment has been completed.

PEDIATRIC AIDS CLINICAL TRIALS

Mr. NATCHER. How many pediatric AIDS centers will be supported in your 1991 budget, Doctor, and at what total cost?

Dr. ALEXANDER. There are 28 pediatric AIDS sites that will be supported in the NICHD clinical trials network.

The total amount of funding for pediatric AIDS is $24.5 million in the 1991 request. The amount of that for the pediatric AIDS clinical trials sites is approximately $5 million.

Mr. NATCHER. What links do these centers have with the Health Resources and Services Administration Pediatric AIDS Services demonstrations?

Dr. ALEXANDER. We have encouraged that linkage to develop. Not all of the centers are funded in places where these centers from the HRSA are also present. Where they are present, we have

encouraged the development of networks so that comprehensive care is offered in conjunction with our trials.

We also, in places where these don't exist, have encouraged the investigators to offer a program of comprehensive care in conjunction with the clinical trial that is under way.

We have been extremely successful in this, and even though these trials are offered to a high-risk group of children who are living in conditions associated with poor medical care, with usual poor compliance, we have been successful in achieving a 95 percent compliance rate with our particular clinical trial. Much of that success is due to the fact that they are offered compassionate, caring, and comprehensive care in conjunction with their participation in the clinical trial.

CHILD HEALTH RESEARCH CENTERS

Mr. NATCHER. Members of this subcommittee have been concerned with your starting up new Child Health Research Centers at the expense of existing centers. How much funding was transferred from existing centers to support the new ones?

Dr. ALEXANDER. No funds were transferred from existing centers. Two million dollars was added by Congress to the NICHD appropriation for the purpose of establishing this new centers program.

Those funds are the funds that will be used for starting the new Child Health Research Centers.

Mr. NATCHER. How much will the new centers cost, Doctor? How much will each center cost?

Dr. ALEXANDER. We have capped the cost on these centers at $400,000, total costs.

We have indicated the specific purposes for which these funds may be used by the centers. They will be used in part to fund core laboratories, but primarily to support young investigators developing pilot studies and receiving career development enhancement under the tutelage of mentors in these particular centers.

So the cost for each center will be a maximum of $400,000. We anticipate funding five or possibly six centers under this program in this fiscal year.

Mr. NATCHER. Doctor, why not fund a smaller number of new centers instead of cutting back on existing centers?

Dr. ALEXANDER. Mr. Chairman, this is a decision that we weigh carefully every year when we submit our budget request. Some years we have proposed cutting back on the number of centers when negotiated reductions on the centers loom particularly large.

When we have proposed that in the past, the committees' direction to us has been to continue the number of existing centers, and additional funds have generally been provided to make up for the differences.

This particular year our decision once again was to go with the existing number of centers. We have a very high level of negotiated reduction, but our feeling was that these centers are all important; they are working in important areas. The addition of the child health centers was felt to be extremely important for the pediatric community and for the development of the next generation of investigators. For that reason, it was a difficult decision but we chose

to go with maintaining the existing centers, adding the new Child Health Research Centers, and adding one learning disability center as directed by the committees.

Mr. NATCHER. Mr. Stokes, I yield to you.

Mr. STOKES. Thank you, Mr. Chairman.

Dr. Alexander, your fiscal year 1990 budget was $442.9 million, and you are requesting $461.5 for fiscal year 1991, which would represent an increase of $18.6 million; is that correct?

Dr. ALEXANDER. That is correct.

INFANT MORTALITY RANKING

Mr. STOKES. Now, two of the priorities within your institute are infant mortality and improving minority health. Is that correct?

Dr. ALEXANDER. Yes.

Mr. STOKES. How do we compare with other nations in the world in terms of infant mortality?

Dr. ALEXANDER. The United States' ranking is presently 20th in international comparisons of infant mortality.

Mr. STOKES. And, in fact, in some parts of the United States our rate is worse than that of some Third World countries, isn't it?

Dr. ALEXANDER. That is correct.

Mr. STOKES. Now, in the area of infant mortality, which is now a national priority, how much of your budget is targeted towards infant mortality?

Dr. ALEXANDER. The 1991 request includes $61.4 million for infant mortality research.

MINORITY HEALTH

Mr. STOKES. In the area of improving minority health, what part of your budget is designated for that?

Dr. ALEXANDER. Because so many of our programs relate to minority health, infant mortality being the flagship of those, it is difficult to say exactly how much is targeted to minority health.

The figures that I do have overall, including minority health and assistance, total $81.2 million.

Mr. STOKES. All right. I would appreciate if, for the record, you would develop for me the number of your programs targeted toward improving minority health and the amount and percentage of your budget being expended for that purpose.

Dr. ALEXANDER. I would be pleased to do that, Mr. Stokes.

[The information follows:]

IMPROVING MINORITY HEALTH

The following NICHD programs have a significant impact on improving minority health:

Low Birth Weight/Infant Mortality; Prevention and Treatment of AIDS and other Sexually; Transmitted Diseases; Adolescent Pregnancy; Sudden Infant Death Syndrome; Drug Abuse in Pregnancy; and Infant Day Care

In addition, the NICHD has earmarked approximately 1 percent of competing research project grant dollars for administrative supplements for the support of underrepresented minority scientists and students, to participate in research under a vairety of projects supported by NICHD grants.

In FY 1991, it is estimated that the NICHD will spend approximately $81.2 million, or 17.6 percent of the overall budget, on programs for minority health and assistance.

PEDIATRIC AIDS

Mr. STOKES. Doctor, how many children are infected with the AIDS virus currently?

Dr. ALEXANDER. At the present time we have had reported about 2500 children and adolescents with AIDS. That is full-blown AIDS.

Our estimate of the number infected by the end of this year is about 20,000.

Mr. STOKES. Do you anticipate an increase or a decrease in the numbers of children with AIDS?

Dr. ALEXANDER. There is no question but that that number is going to increase.

There is a large reservoir of infected women of child-bearing age who are going to bear children who are going to be infected with this virus. This is not an epidemic that has peaked; this is not an epidemic that is going away. We are going to see steadily increasing numbers of children with AIDS, almost entirely as a result of maternal to fetal transmission.

Mr. STOKES. Then we should not believe these recent media reports that the incidence of AIDS is decreasing in some populations?

Dr. ALEXANDER. I think it is correct, as you qualify it, in some populations. There are indications that the rate of increase of incidence may be tailing off due to some changes in sexual practices and possibly due to effectiveness of treatment, but that is only a change in rate of increase. It does not mean a decrease. I think it is important to keep that in mind.

Also, the population that was addressed in that particular study was not the population of children. That epidemic has yet to come anywhere near its peak. It is going to increase very steadily.

HIGH RISK BEHAVIORS

Mr. STOKES. Doctor, I understand that there is considerable research being conducted on drug abusers, prostitutes and others who engage in behaviors that put them at extremely high risk of HIV transmission.

While these groups include minorities, they are not representative of the vast majority of minority group members.

Can you tell us what studies the institute has planned to obtain more information on AIDS in the larger minority community?

Dr. ALEXANDER. Mr. Stokes, that is one of the reasons that our feasibility study for a national Survey of Health and AIDS Risk Prevalence is so important. Most of the studies of AIDS behavioral risk are done in areas where the population is viewed at high risk, such as drug users in urban areas. Minorities are over-represented in these studies and the impression can be left that these studies describe minority behavior.

Even our feasiblity study—the Survey of Health and AIDS Risk Prevalence—is a population-based study. It will not target specifically high-risk populations because it is a national, population-based sample. This is the only way that we will be able to get at indications of risk for the whole population—minority and majority alike. This is the only way that we will be able to get at indications of the prevalence of some of these behaviors for the whole population.

This survey will give us an indication of the prevalence of some of these risk behaviors in minorities as they are represented in the entire population, not just in high risk areas. That is why this study is important for projections of the epidemic. Also, for educational efforts and programs to lower risk behaviors it is important to know how these behaviors are distributed across the population.

I think it is important, regarding the minority population, to have a broader picture of the distribution of these risk behaviors, and not rely on information that comes from special populations that are not representative of the population as a whole. By assessing the risk behaviors on the populations as a whole, we get a truer picture of what is going on.

Mr. STOKES. That is exactly what I had in mind.

To what extent have you included minorities in your clinical trials?

Dr. ALEXANDER. Our population that is involved in the clinical trial in AIDS is approximately 85 percent minority, both black and Hispanic.

We have made efforts to locate the centers for these particular trials in areas of high prevalence of children with AIDS, and we have, as a consequence, a population that is largely Hispanic and black. That population is being served well by these particular clinical trials. They are receiving fairly comprehensive medical care and social services and support services in conjunction with their participation in that trial.

AIDS IN ADOLESCENTS

Mr. STOKES. To what extent are adolescents represented in pediatric AIDS clinical trials?

Dr. ALEXANDER. Adolescents are vastly under-represented, unfortunately. This is a population that is very difficult to reach. It has been difficult to recruit adolescents into these trials.

Adolescents represent an under-recognized source of infection and transmission of AIDS. Although only about 500 adolescents have been identified with AIDS, in the population overall with AIDS, about 20 percent occurs in people in their 20s, and chances are that most of them were infected during adolescence, so adolescence is a time of high risk of transmission and acquisition of this infection.

It makes it extremely important for us to target our educational and intervention efforts toward the adolescent population. And it also is important for us to try and increase our efforts to recruit adolescents into the clinical trials. We need to do a better job of this than we have in the past.

CRACK BABIES

Mr. STOKES. Doctor, can you tell us what the consequences are for an infant born to a mother who has abused drugs during her pregnancy? I am particularly interested in the use of crack cocaine during pregnancy. Tell us what research you are doing in this area.

Dr. ALEXANDER. Mr. Stokes, this is a rapidly increasing problem that threatens very seriously to reverse our nation's downward

trend in infant mortality, and probably is partly responsible for the slowing in decline of that infant mortality rate.

This is an epidemic that is having a significant impact on mothers and infants. There is clear evidence now that use of cocaine by the mother during pregnancy does damage the fetus. It is not a passive and transient phenomenon that disappears after the newborn nursery course, which is complicated by cocaine withdrawal, but also has long-term mental consequences for that infant.

There is pretty good evidence that these infants, when they become school children will have difficulty learning. Their behavior is abnormal and aberrant in many cases, and we are just starting to learn the long-term adverse effects of cocaine use during pregnancy.

A recent survey was done just in 12 cities that identified almost 10,000 infants born in the last year to cocaine-addicted mothers. The long-term implications of this I think we are just starting to appreciate.

The research that the institute is doing includes epidemiologic efforts to try to identify the extent of this problem and longer-term follow-up studies to try and give us an indication of just what the longer-term consequences are going to be, and also beginning efforts to try and develop effective ways to withdraw a pregnant woman from cocaine during her pregnancy.

The standard teaching has been that there is not a safe way to withdraw the pregnant woman from cocaine without damaging the fetus. That may have been satisfactory before we knew that the cocaine itself was damaging the fetus. It is no longer acceptable.

We have to develop both behavioral and medical means of encouraging women to get off of cocaine during pregnancy and an effective way to withdraw them. The institute will be working in that area.

Mr. STOKES. Mr. Chairman, I have a number of other questions to ask Dr. Alexander, but I will just——

Mr. NATCHER. Go right ahead for awhile. Go right ahead, Mr. Stokes.

RESEARCH ON DAY CARE

Mr. STOKES. Okay.

Doctor, you mentioned in your opening statement that your Institute has launched a major cooperative clinical study of the emotional, social and intellectual development of children in day care situations.

First, tell us, will this project include broad geographic, socioeconomic and ethnic representation in the day care settings and children under study?

Dr. ALEXANDER. One of the objectives of this study, Mr. Stokes, has been to do exactly that, to provide a broadly representative population that includes geographic diversity, socioeconomic diversity, and racial and ethnic diversity. We have a large enough population so that sub-sample analyses will be possible.

We followed this committee's directive and expanded this study to include 10 different sites where this study will be done so that

we can recruit the full number of children; that is 1200, originally projected as necessary for this study.

With this number of children and this diversity of sites, we will be able to get that type of population and do the subset analyses that are so important.

Mr. STOKES. What is your time frame for completing this study, Doctor?

Dr. ALEXANDER. Intake of subjects will begin probably in June, and the study is designed to run with three years of data collection and then a year-and-a-half of data analysis.

Mr. STOKES. And how much funding are you requesting for fiscal year 1991?

Dr. ALEXANDER. For fiscal year 1991 the day care network request is $3.8 million.

INJURY PREVENTION

Mr. STOKES. Doctor, I understand that accidents are the leading cause of death of young children in our country. What is the status of your five-year research plan on accident prevention?

Dr. ALEXANDER. That plan is proceeding pretty much on target, Mr. Stokes. We have presently funded about 15 projects that have been supported as a result of this particular research initiative. We have issued requests for applications as well as contracts as called for in that plan.

We have been using particularly effectively, I think, the Small Business Innovation Research Program in order to support the development of new technologies for injury prevention. That program request in fiscal year 1991 is $2.1 million.

Mr. STOKES. Will you be able to complete the studies within the time frame that was established?

Dr. ALEXANDER. We are probably going to run a year or so behind that original projection.

SIDS

Mr. STOKES. Doctor, to what extent does sudden infant death syndrome contribute to infant mortality in our Nation?

Dr. ALEXANDER. Sudden infant death syndrome is a major factor in our Nation's infant mortality rate. It is the leading cause of death between one month and 12 months of life, and it accounts for probably 7,000 infant deaths a year out of the 38,000, so it is a major problem.

Mr. STOKES. Now, you have a five-year sudden infant death syndrome research plan, do you not?

Dr. ALEXANDER. Yes, at the direction of the Congress, the Institute consulted broadly with the scientific community and developed a five-year research plan for SIDS research.

Mr. STOKES. What funds are requested to implement the second year of the five-year plan for fiscal year 1991?

Dr. ALEXANDER. The request for the second year of the implementation of the five-year plan is $5,200,000.

PERSONNEL APPOINTMENTS

Mr. STOKES. Okay.

Doctor, I have another question that you can answer in the record. I would want you to expand upon it. I will just read the question at this time, then you expand upon it.

NICHD relies very heavily upon appointments for its scientists. When scientists are appointed, is there any process for evaluating their performance and to determine their qualifications for reappointment? To what extent is the decision to renew a contract made on the basis of merit, as is required by the Civil Service Reform Act?

For instance, is there a formal, written administrative procedure for evaluation as a basis for reappointing, transferring, and terminating scientists? If so, is there a grievance procedure if they disagree with your evaluation, and can you cite specific provisions governing these issues?

Dr. ALEXANDER. We will be pleased to supply that for the record, Mr. Stokes.

[The information follows:]

PERSONNEL PROCEDURES

Question. NICHD relies heavily on appointment of scientists. When scientists are appointed is there any process for evaluating performance to determine qualifications for reappointment?

Answer. NICHD scientists are appointed under several different personnel systems and authorities involving different requirements for performance evaluation.

Scientists appointed in the U.S. Public Health Service *Commissioned Corps* receive an annual Commissioned Officers' Effectiveness Report. Appointments are continuing, without requirement for reappointment. Officers' must maintain at least a satisfactory level of performance to remain in the Corps.

Scientists appointed in the *Civil Service* receive evaluations under the Senior Executive Service (SES), Performance Management and Recognition System (PMRS), or Employee Performance Management System (EPMS), each of which systems requires an annual written plan, interim review, and final appraisal of performance. While employees must maintain at least a minimally satisfactory level of performance, most appointments are permanent and do not require reappointment. Temporary appointments may be extended, but depending more upon program needs for the function than upon performance evaluation of the temporary employee.

For *non-tenured appointments*, such as Experts, Visiting Associates and Scientists, and Staff Fellows, there is no separate process for evaluating performance. However, formal NIH policy requires assessment of performance, in addition to determination of program needs for the function, as part of the justification for extension of these temporary appointments within the limits of the respective appointment authority.

Question. To what extent is the decision to renew a contract made on the basis of merit as is required by the civil service reform act [CSRA]? For instance, is there a formal written administrative procedure for evaluation of a basis for reappointing, transferring, and terminating scientists?

Answer. As described above, employees serve on a number of types of personnel appointments, rather than on contracts. For scientists who serve on time-limited appointments, the decision to renew is based primarily upon program needs for the function and secondarily, upon the scientists' level of performance.

The Civil Service Reform Act (CSRA), codified in various sections of Title 5 of the United States Code, does not pertain to contract renewals. Instead, this statute addresses career appointments and procedures for removal from such appointments. Therefore, the protections provided by the CSRA do not apply to temporary appointments such as Visiting Scientists, Staff Fellows, or Special Experts which are subject to annual renewal.

Specific performance evaluaton procedures are written for the Commissioned Corps and regular Civil Service employees but not for non-tenured employees. There is a provision for assessing performance of non-tenured employees in the NIH written procedure for justifying extension of their appointments. For all employees, performance evaluations are used in the full range of personnel management decision-making, including renewal or extension, reassignment, and separation.

Question. If so, is there a grievance procedure if they disagree with this evaluation?

Answer. Yes, all NIH employees are covered by grievance proedures and may grieve their performance evaluations. The separate EEO complaints process is also available to employees who allege discrimination in management decision-making.

Question. Can you cite specific provisions governing these issues?

Answer. Yes. The governing provisions are:

Regular Civil Service employees are covered by 5 U.S.C. 3101 and Chapter 51 of that Title, and 5 U.S.C. 4314.

Special Expert appointments are under authority of 5 U.S.C. 3109 and 42 U.S.C. 282(d).

Visiting Program appointments are under authority of 42 U.S.C. 209.

Staff Fellow appointments are under authority of 42 U.S.C. 209.

Commissioned Corps appointments are under authority of 42 U.S.C. 204.

NIH Grievance Procedures are covered by DHHS Personnel Instruction 771-3.

Mr. STOKES. Thank you very much, Dr. Alexander.

Thank you, Mr. Chairman.

Mr. NATCHER. Dr. Alexander, we want to thank you and your associates for appearing before our committee at this time on behalf of your budget request for the fiscal year 1991. It has been a good hearing, Doctor. Thank you very much.

Dr. ALEXANDER. Thank you, Mr. Natcher.

[The following questions were submitted to be answered for the record:]

CONTRACEPTIVE RESEARCH

Mr. Natcher. How much contraceptive research is being conducted in foreign countries compared to the efforts you support in this country?

Dr. Alexander. We do not have information about the contraceptive research being conducted by pharmaceutical companies in foreign countries. However, many foreign governments provide funding for contraceptive development research through support of United Nations agencies. Of the $182 million provided to the Human Reproduction Programme (WHO) by national governments and other donors between 1970 and 1986, the U. S. contributed only $3.2 million. The NICHD program of contraceptive research is supported at the level of $20,500,000 in FY 1990.

PEDIATRIC AIDS

Mr. Natcher. How many new cases of pediatric AIDS are expected to be identified in each of the next several years?

Dr. Alexander. In 1988, a study jointly conducted by the NICHD and the CDC determined that approximately 5,600 women gave birth who were HIV-infected. In 1989, this number of infected pregnant women giving birth is placed at about 6,400. Approximately one-third of the children born to infected women will themselves be infected. Thus, these two years alone will give us over 4,000 children who will ultimately die of AIDS. Some of these children will develop full-blown AIDS early in life. Others will follow a more quiescent course until their infection becomes clinically evident.

CHILD HEALTH RESEARCH CENTERS

Mr. Natcher. Why did you interpret conference report language which "encouraged" you to "consider" establishing these child health research centers as a mandate?

Dr. Alexander. The NICHD consistently follows report language -- House, Senate, and Conference reports -- as closely as possible to respond to Congressional intent. The report language in the FY 1990 Senate report identified a $2 million increase over the FY 1990 House allowance ".. for the purpose of establishing a center grant program to encourage the growth of centers for child health research." These centers were first mentioned at the House Appropriations Subcommittee hearings when two members of the subcommittee raised the subject. Subsequently, the Senate Allowance, including the $2 million increase, was agreed to by the House/Senate conferees. In addition, the conference report language referred to the Senate report for guidance on establishing a center grant program for child health research. Again, it is NICHD policy, consistent with policies of DHHS and NIH regarding report language, to honor the intent of the Congress to the extent possible.

Mr. Natcher. What areas of basic science do you expect these centers to study?

Dr. Alexander. We expect the new Child Health Research Centers to focus on many of the basic science themes relevant to the NICHD

responsibility to study physical and mental development. These include molecular biology and genetics, immunology and infection, nutrition and tissue maturation, endocrinology, behavior, and growth.

MENTAL RETARDATION RESEARCH CENTERS

Mr. Natcher. How many mental retardation research centers would be funded in 1991?

Dr. Alexander. There are 12 mental retardation research centers that will be funded in FY 1991.

Mr. Natcher. Will any be up for recompetition in 1991?

Dr. Alexander. There are two mental retardation research centers scheduled for competing renewal in FY 1991.

RESEARCH PROJECT GRANTS

Mr. Natcher. Why are you projecting a steady drop in the number of research grant applications from 1988 to 1991?

Dr. Alexander. Projections of the number of NICHD research project grant applications are initially made by the Division of Research Grants using previous years' data. The drop in anticipated grant applications for FY 1990 and FY 1991 represents the continuation of a downward trend that began in FY 1986, when 2,048 applications were received, followed by: FY 1987, 1,642; FY 1988, 1,829; FY 1989, 1,762. We are not certain about why the numbers are on a decline, but one explanation is the difficulty that even well-established research investigators have experienced in competing successfully for available grant dollars.

CLINICAL TRIALS

Mr. Natcher. How many clinical trials are included in your 1991 request and how much would they cost in total?

Dr. Alexander. We are estimating 107 clinical trials for FY 1991 at a total cost of $35 million.

Mr. Natcher. Do you propose any new starts in 1991?

Dr. Alexander. Yes. Three new major clinical trials are proposed -- two AIDS and one Non-AIDS, with a cost of $1.13 million.

SUDDEN INFANT DEATH SYNDROME

Mr. Natcher. Provide for the record a table describing estimated resources throughout the Department for sudden infant death syndrome in 1989 to 1991.

Dr. Alexander. Estimated resources for SIDS at NIH are as follows:

Sudden Infant Death Syndrome

NIH	1989 (Actual)	1990 (Est.)	1991 (Est.)
NICHD	$35,674,000	$37,961,000	$39,400,000
NINDS	2,870,000	2,962,000	3,098,000
NCRR	800,000	844,000	840,000
Total	39,344,000	41,767,000	43,338,000

SURVEY OF HEALTH AND AIDS RISK PREVALENCE

Mr. Natcher. How much funding is available in either your 1990 or 1991 budget for either of the two studies of sexual behavior you have pre-tested? How much funding was used for the pre-tests of each?

Dr. Alexander. The Survey of Health and AIDS Risk Prevalence (SHARP) is a study of adults. The contract to develop the instruments, design a sample and prepare a research strategy was funded in FY 1988 for $492,000. The funds to conduct a feasibility study ($1.5 million) were also committed in FY 1988. The feasibility study has been delayed and there will be additional cost for completion. There is no plan for a full scale study and there will not be one until we have had the opportunity to assess the results of the feasibility study. Therefore, there are no funds in the FY 1990 or FY 1991 budget for the full scale study of adults.

The American Teenage Study represents the culmination of many years of investment into research on adolescent fertility-related behavior, behavior which for some adolescents puts them at risk of HIV infection. This project will be conducted under a research project grant that includes both a pretest and the full study. The project has passed scientific peer review and advisory council review. The total costs are $16 million over a five year period. However, since a starting date has not been determined it is not possible to say how much of the costs will come from FY 1990 and FY 1991. The funds for this study will come from the NICHD grant budget.

FY 1991 BUDGET REQUEST

Mr. Conte. Dr. Alexander, what was your initial budget request?

Dr. Alexander. The initial budget request for FY 1991 from NICHD to NIH was $712,536,000.

CURRENT SERVICES BUDGET

Mr. Conte. What additional funds are necessary to maintain current services?

Dr. Alexander. The FY 1991 current services budget for NICHD is $500,476,000. An additional $39,003,000 above the FY 1991 President's Budget would be required.

DOWNWARD NEGOTIATIONS

Mr. Conte. What is your anticipated downward negotiation rate with this budget?

Dr. Alexander. The estimated downward negotiation rates for NICHD in FY 1991 are: noncompeting research project grants--15.5 percent; competing research project grants--12.0 percent; research centers--21.6 percent.

USE OF ADDITIONAL FUNDS

Mr. Conte. If more funds were allocated to your Institute, where would you put the money?

Dr. Alexander. Additional funds would be used first to lower or even eliminate the downward negotiations in research project grants and centers. Other funds would support additional research project grants with an objective of attaining a 40 percent funding rate; add seven new research center grants which would include two in mental retardation research, two in population research, and three additional child health research centers; support additional research career awards, and expand the Institute's cooperative clinical research networks; provide support for more research training positions, and provide more funding for R&D contracts. These increases would allow for expansion of research efforts in pediatric AIDS, drug abuse in pregnancy, contraceptive development and evaluation, SIDS, infant mortality, teenage pregnancy, and vaccine development.

IMPACT OF SEQUESTRATION

Mr. Conte. What has been the impact of last year's sequester at your Institute?

Dr. Alexander. The FY 1990 sequester for NICHD was $6,173,000 which represented a reduction of approximately 1.4 percent of the FY 1990 Appropriation. Since the reductions were taken essentially across-the-board, all budget mechanisms and Institute programs were affected to some extent.

DECADE OF THE BRAIN

Mr. Conte. As you know, the Decade of the Brain is now well underway. Institutes all over NIH are planning cooperative ventures in neuroscience research. With the explosion of knowledge in the field of neurological development in the growing fetus and infant, I think this is a terrific opportunity for your Institute to get involved in the Decade of the Brain. What are the major opportunities in pediatric neurology, and developmental neurobiology in the coming Decade?

Dr. Alexander. The adult nervous system contains millions of cells all of which form a network of very specific connections. How appropriate cells arise and make their correct functional connections has been an area of intense investigation for many years. Major technological breakthroughs have occurred in molecular biology and cell biology over the past five years which have important ramifications for studying the development of the nervous system. These advances now permit us to identify individual genes which are necessary for normal development of the nervous system, and for its appropriate wiring. We also now have the technology in hand to modify these genes in very specific ways and introduce these altered genes into living embryonic stem cells. Such molecularly manipulated cells can be used to produce transgenic animals which will serve as models for human central nervous system birth defects and to identify the pathological pathways in the developing nervous system. Tailor-made animal models for human conditions can be utilized to identify individual molecules which are vital for normal development. These technical advances will allow us to address the mechanisms regulating normal development, and conversely, recognize the mechanisms by which congenital defects of the central nervous system are produced. Birth defects, such as spina bifida, which have multifactorial origins can now be addressed using such animal models.

Mr. Conte. Are you planning to join your fellow Institutes in participating in the Decade?

Dr. Alexander. Yes. We are already participants in the NIH planning activities centering on the Decade of the Brain.

PEDIATRIC AIDS

Mr. Conte. Doctor, as you know, the incidence of pediatric AIDS continues to rise. Over 2,000 children have died so far, and if the present rate continues, AIDS will become a major contributor to childhood deaths in the near future. What is your Institute doing in the field of pediatric AIDS?

Dr. Alexander. Our Institute is conducting and supporting research on a wide range of topics in the field of pediatric AIDS. For example, we

1. conduct together with the NCI a study of the vertical transmission of HIV from mother to child

2. conduct together with the NCI a study of the impact of HIV on the neurological status of infected children

3. conduct together with the CDC a study of the prevalence of HIV infection in childbearing women in the United States

4. conduct together with the CDC and the National Hemophilia Foundation a study of the natural history of HIV infection in infected hemophiliac children

5. conduct the largest clinical trial in the world involving HIV-infected children and are currently amalgamating our efforts with those of NIAID to continue work in the clinical trials area

6. support research in a wide variety of areas in pediatric AIDS including the early diagnosis of HIV infection in infants and children, the role of the placenta in the transmission of HIV infection from mother to child, the epidemiology of HIV infection in mothers and children in Africa, the role genetics may play in the transmission of HIV infection from mother to child, and a number of other important areas.

Mr. Conte. How much does the budget provide for pediatric AIDS for your Institute?

Dr. Alexander. The FY 1991 estimate for pediatric AIDS is $24,500,000.

Mr. Conte. Are there projects not funded in the budget request? What are they?

Dr. Alexander. Yes. The following projects are not funded in the FY 1991 budget request:

Therapeutic research in pregnant animal models ($1,000,000)

Expansion of HIV studies: (1) laboratory and clinical markers of HIV progression in infants and children; (2) immunopathogenesis of HIV infection and disease in infants and children ($2,500,000)

Expansion of maternal and pediatric Phase I, II, and III clinical trials ($17,900,000)

Expansion of international pediatric and maternal therapeutic research ($5,000,000)

Establishment of antenatal, inpatient therapeutic units ($3,500,000)

Behavioral aspects of maternal, adolescent, and pediatric HIV disease ($750,000)

Research in adolescent HIV disease ($750,000)

Human milk in the transmission of HIV infection ($750,000)

Mr. Conte. In your professional judgment, how much should be spent on pediatric AIDS?

Dr. Alexander. The FY 1991 professional judgment figure for NICHD efforts in pediatric AIDS is $47,600,000.

DOWNWARD NEGOTIATIONS

Mr. Conte. Doctor, how many years have you had to use downward negotiations?

Dr. Alexander. The NICHD began downward negotiations for research project grants and research centers in FY 1986, and reductions have been imposed in each subsequent year. Counting FY 1991, downward negotiations will have been used for six years.

Mr. Conte. In your professional judgment, how much funds would you need in the FY 91 budget to restore your awards to full funding levels?

Dr. Alexander. To restore all research project grants and research centers to full cost in FY 1991 would require $55,008,000 above the President's budget.

PRE-ECLAMPSIA

Mr. Conte. Pre-eclampsia, or high blood pressure during pregnancy, is one of the great mysteries in obstetrics. It is the third leading cause of maternal morbidity and a major cause of fetal growth retardation and post-birth mortality. There was a study which linked barrier contraceptives with pre-eclampsia. Can you comment on the clinical implications of this study?

Dr. Alexander. The clinical implications of this study depend on the validity of the study, the corroboration of its findings with other studies, and the biological plausibility of the results. An analysis of these issues suggests that further studies need to be done before the results of this study can become part of clinical practice.

The biological plausibility of the hypothesis is doubtful. The authors postulate that prior exposure of the uterus to the partner's sperm reduces the probability of preeclampsia during a subsequent pregnancy. They then assume that the use of barrier contraception precludes any intrauterine exposure and that barrier users should experience higher rates of preeclampsia as a result. However, users of oral contraceptives also do not experience intrauterine exposure to sperm because of their thickened cervical mucus, and users of natural family planning prevent this occurrence by avoiding intercourse during the time of the cycle which permits sperm to ascend to the uterus. The lack of increased preeclampsia in users of these methods refutes the mechanism suggested.

Several errors in methodology discount the validity of this study -- variable response rate between cases and controls and the manner in which barrier use was determined. The authors made no effort to determine consistency of use. They made the assumption that barrier users used their methods at every intercourse during

every month for which they were considered barrier users. The high rate of accidental pregnancy among barrier users disproves this assumption. The authors could have better supported their claim if they had measured consistency of barrier use and reported the results of a dose-response analysis (i.e., Did those women using barriers more consistently have a higher risk of preeclampsia than women using barriers sporadically?). The authors also did not adequately explain why the reputed effect of barriers held for single women only but not for married women. Marital status should not have such a profound and opposite effect on the outcome if the study hypothesis is true.

Mr. Conte. Would you modify recommendations regarding contraception based on the findings of this report?

Dr. Alexander. No modification in recommendations concerning contraceptive practice can be made as a result of this study at this time. As the authors of the paper state, theirs is the first attempt to investigate the relationship between preeclampsia and contraceptive methods. Hence, no corroborating data exist. A change in clinical practice usually requires at least two good studies supporting the change. The problems evident in this first study as well as the lack of corroborating evidence suggest that further work must be done before any recommendations can be made about contraceptive use.

Mr. Conte. What research is being done on pre-eclampsia at NICHD?

Dr. Alexander. Preeclampsia, a hypertensive syndrome that is uniquely associated with pregnancy, affects 5 percent or more of pregnancies and places the mother and fetus at higher risk of morbidity or even mortality, if symptoms are discovered late or neglected.

For several years, NICHD has supported research grants on preeclampsia and other forms of hypertension in pregnancy. About 3 years ago, the Institute strengthened its commitment to the understanding and management of preeclampsia through a joint effort with the National Heart, Lung, and Blood Institute. This initiative resulted in the funding of 18 new research grants on a broad range of approaches to understanding the disease, ranging from cellular and subcellular mechanisms, to systemic pathophysiology, to prevention.

In addition, the Maternal-Fetal Medicine Units, a network of research units established by NICHD four years ago has initiated a major clinical trial designed to prevent preeclampsia. This trial is studying the effectiveness and safety of giving a very low-dose of aspirin (60 mg.--baby aspirin strength) daily to healthy women in their first pregnancies, who are at above-average risk of developing preeclampsia. This study is well over one-third along toward its goal of assessing 3,000 patients. Sub-studies are also being done that may allow better prediction of which patients may benefit the most from such aspirin therapy.

EFFECTS OF PHENOBARBITAL ON INTELLECTUAL DEVELOPMENT

Mr. Conte. Doctor, I read about that worrisome study which suggests that a commonly used drug for childhood seizures, phenobarbital may impede intellectual development. Can you shed light on this study?

Dr. Alexander. The aim of the study was to determine whether phenobarbital indeed provided protection from febrile seizures in children and whether prolonged administration produced side effects in these children. The study was informative in that it demonstrated that important developmental changes are occurring within the child's brain during the first five years of life, and that, as with any therapeutic agent, we must consider changes in the normal chemical milieu of the brain which may alter normal function. As our ability to assay developmental changes becomes more sensitive we will have to reassess the administration of known treatments for their potential harmful effect.

LEARNING DISABILITIES CENTERS

Mr. Conte. As you know, the Committee provided funds last year for a third learning disability center. Where do things stand in the development of that 3rd center?

Dr. Alexander. Competitive applications for this third center grant will undergo scientific peer review written the next couple of months. We anticipate making the grant award by late summer or early fall, 1990.

Mr. Conte. Can you tell us what progress the first two centers have made?

Dr. Alexander. The Learning Disabilities Centers at Yale University and the Johns Hopkins University are beginning to recruit children and adults with learning disabilities and contrasting disabilities. When these individuals have been recruited, studies of their biological and behavioral characteristics will be initiated. From these studies, basic information on the cause(s) of learning disabilities will be determined. Some interesting findings should be forth coming during the five year period of these awards. While no answers should be expected immediately, the Yale Center has a clear focus of clarifying the classification of learning disabilities, attentional deficits, and several other disorders of childhood. This effort should pay dividends for scientists who do not have the resources to collect large samples of individuals with learning disabilities because they will be able to use the criteria developed at the Yale Center for better defining their research sample populations. The Learning Disabilities Center at the John Hopkins University has begun to collect important brain behavior relationships from a variety of individuals with genetic abnormalities that manifest themselves in behavioral patterns similar to those individuals with learning disabilities with unknown etiologies. State-of-the-art brain imaging technology and neuropsychological measures are being developed to attack the mysteries of learning disabilities.

MENTAL RETARDATION

Mr. Conte. Your Institute supported a study which looked at morbidity and mortality rates for individuals with mental retardation at different residential settings. Can you tell us the basic findings of that study?

Dr. Alexander. A study of mortality rates for three different age groups of individuals with mental retardation was made for the purpose of determining factors that predict high mortality. The three age groups were young (0 -20), adult (21 -54), and elderly (over 55). This study was based on a sample population of individuals with mental retardation who resided in the State of California during the period of 1984 to 1987. The types of residence considered in this study were: own home, independent, institutions, skilled care nursing, health facilities, community care, small group homes, others, and unknown. Of all these residence types, skilled care nursing facilities demonstrated the highest mortality over all ages. Institutions and health facilities were the nexc most frequent residence type with high mortality. The three factors most predictive of early mortality are functional limitations in feeding, toileting and mobility. Specific diagnostic categories within mental retardation have different mortality rates at different ages. For example, individuals with Down syndrome have relatively low mortality in the 0 to 54 age group but have a high mortality after age 55.

Mr. Conte. What are the implications of this data?

Dr. Alexander. Individuals who are mentally retarded and have functional limitations in mobility, feeding and toileting need more care than those who are less functionally limited. The type of care needed influences the place of residence. Those with multiple limitations are most likely to reside in skilled care nursing, institutional or health facilities. This study did not examine the type of care provided for the different functional limitations of those residents with mental retardation living at skilled care nursing facilities. This study makes clear that there is a need for research scientists to turn their attention to developing effective treatments for mobility, feeding and toileting limitations for use in skilled care nursing, institution and health care facilities. These treatments could be adopted for use in other residential settings (own home, small group homes, apartments, etc.) with the goal of reducing the need to admit individuals with mental retardation and functional limitations to facilities with increased medical care.

VACCINE DEVELOPMENT

Mr. Conte. Tell us what advances are being made at your Institute in the field of vaccine development.

Dr. Alexander. The Laboratory of Developmental and Molecular Immunity, in the NICHD Intramural Research Program, is developing a series of new vaccines. This list includes vaccines to prevent infections with pertussis, Staphylococcus aureus, Pneumococcus type 6 and 12, H. influenza type B, Salmonella typhi and Salmonella type A, Shigella sonnei, flexneri and shigs.

Mr. Conte. What work do you share with the National Vaccine Program?

Dr. Alexander. NICHD scientists maintain contact with the officials of the National Vaccine Program and are planning to collaborate in examining the NICHD pertussis toxoid vaccine.

Mr. Conte. In the long-term, what childhood diseases may be prevented by the development of new vaccines?

Dr. Alexander. Diseases due to the organisms listed above, all serious in young children, will be prevented when the vaccines are fully developed and become generally in use.

ENDOMETRIOSIS

Mr. Conte. Doctor, endometriosis is a serious disease of women that causes substantial pain, suffering and infertility. The cause of this remains elusive. What work is being done to investigate endometriosis?

Dr. Alexander. The natural history of endometriosis has not been fully clarified and we are currently in a perplexed state in regard to the origin, progression, optimal therapy, and prevention of this disease. We also do not have a clear understanding of the cause-effect relationship of endometriosis and infertility. We do know that endometriosis appears to be a spectrum of diseases rather than a single one and that there is a dependent relationship of endometriosis lesions on continuing ovarian function. Our current therapies of surgery or drug treatments have been rationally based on the empirical findings available. Basically, the cessation of ovulation and menstruation most consistently provide improvement to patients with endometriosis.

Work is currently ongoing to expand our understanding of the basic mechanisms of endometriosis cause and progression as well as approaches to suppress or terminate such progression. We have sponsored research that developed an animal model in which the induction and growth of ectopically implanted endometrial tissue mimics the symptoms of endometriosis. This model provides the opportunity to investigate the suppressive effects of certain hormonal states. Other workers are investigating the cause-effect relationship between human ectopic endometrial cell growth and an inflammatory response associated with certain product(s). This work has provided direct evidence for the role of certain factors in stimulating the progression of endometriosis. These findings suggest that the cell mediated immune system response producing the secretion of cytokines (lymphokines and monokines) by leukocytes may be a factor in endometriosis progression. The evidence from this study has supported the hypothesis of a potential new mechanism of influencing endometriosis which is based on an aberrant cellular immune response in affected women.

Mr. Conte. Are there prospects for better treatment regimens?

Dr. Alexander. The NICHD has established , through a series of cooperative agreements, a Reproductive Medicine Network in

institutions that will conduct specialized research in this field. This multicenter network, consisting of five clinical units and one data coordinating center, will begin operations this spring. In Phase 1 (six months) of its activity, the Network will identify issues of importance in reproductive medicine, including infertility and reproductive disorders of the male and female, and classify them by public health need and feasibility. In Phase 2 (six months), common protocols and methods will be designed, and in Phase 3 (48 months), the protocol(s) will be carried out and the data collected. Phase 4 (40 months), which will begin six months after the start of Phase 3 and run concurrently, will involve planning for termination of studies, addition of new protocols, and delineation of future research needs. Research to develop an optimal clinical protocol for the treatment of endometriosis is one of the recognized disorders to be addressed by the Reproductive Medicine Network.

SUDDEN INFANT DEATH SYNDROME

Mr. Conte. Sudden infant death continues to perplex our best scientists. I hope that some key breakthroughs can be made on this devastating disease. Doctor, what are the major theories being considered on the cause of SIDS?

Dr. Alexander. Scientists are working with the conceptual framework that the newborn who later succumbs to SIDS has a combination of deficiencies or vulnerabilities resulting in an infant's failure to adapt to external stresses that characterize its new life ex-utero. Therefore scientists must delineate what characterizes the abnormalities in SIDS infants, how they originated, and how the external stresses induce death.

Based on the pathology of SIDS victims, the maternal and neonatal risk factors, and recordings of the physiology of infants who later succumb to SIDS, scientists have hypothesized that the infants may die from cardiac or respiratory failure during sleep. Furthermore these infants may have an arousal deficit that prevents them from eliciting resuscitative mechanisms that help them awaken and breathe during a life-threatening episode. The pathology and physiology studies provide good evidence that SIDS infants are delayed in maturation of those parts of the nervous system that control cardiorespiratory function during sleep and waking. The challenge is to pinpoint these deficits, understand their origin, and devise ways to identify those babies who have these abnormalities early in infancy.

Mr. Conte. What research is underway at your Institute in looking at SIDS?

Dr. Alexander. We are supporting research in the following areas:

- the effects of chronic oxygen deprivation on respiratory function and arousal in newborn and infant animals and the role of peripheral chemosensing organs on arousal responses;

- quantitative analyses of the maturation of cardiorespiratory control during different sleep states, and the contributions

of circadian rhythm to these functions in SIDS victims and controls;

- o quantitative studies of the morphology and neurochemical composition of the peripheral and central nervous system of SIDS victims and control infants;

- o the cellular, biochemical, and molecular development of those regions of the nervous system that control respiratory organs and cardiorespiratory function, and the effects of hypoxia at the cellular and molecular level;

- o identification of new inherited metabolic disorders that may lead to sudden unexpected death, and the development of screening procedures and interventions for these disorders;

- o mechanisms of action of toxins produced by enteric organisms that lead to sudden unexpected death in animals, and their prevalence in SIDS victims.

FETAL MONITORING AND CEREBRAL PALSY

Mr. Conte. There was a recent study which suggested a link between the use of fetal monitors and the subsequent development of cerebral palsy. Can you share with us the potential implications of this study?

Dr. Alexander. A article in the New England Journal of Medicine (1990; 322:588-93), found that electronic fetal monitoring did not improve neurological development in children born prematurely as compared to a similar group monitored periodically by stethoscope. The incidence of cerebral palsy was found to be higher in the electronically monitored group.

This is the only study to suggest an association between electronic monitoring and cerebral palsy (CP). Of course, normal term infants comprise the majority of CP, so that this study of premature infants may not apply to most situations. Also, the rates of CP in this study were higher than those described by other investigators for similar premature infants. Finally, results from a single study are rarely conclusive. Other studies will be needed to assess these associations.

In general, the overall findings are consistent with the current recommendation on fetal monitoring by the American College of Obstetricians and Gynecologists. This recommendation is that electronic monitoring is not superior to intermittent use of stethoscope performed consistently and periodically, every 15 minutes in the first stage of labor, and every 5 minutes during the second state of labor.

A practical problem in many hospitals is that such intense stethoscope monitoring may not be feasible with current nursing availability. In such situations, electronic monitoring may well be superior to what would otherwise be available. It is also true that electronic fetal monitoring is often selected by physicians for medical-legal defensive reasons.

The probable impact of this article upon clinical practice will be to reinforce current professional society recommendations, as modified by local circumstances. Additional research studies will probably be stimulated.

MATERNAL NUTRITION AND BIRTH DEFECTS

Mr. Conte. What is the current state of knowledge regarding maternal nutrition and birth defects? I hear that vitamins with folic acid are said to reduce the chances of having a baby with spina bifida or other neural tube defects.

Dr. Alexander. Recent studies have suggested that vitamin supplementation may reduce the incidence of spina bifida. Though the results have not been conclusive, strong evidence points to the need for adequate nutrition during the time of conception. This is particularly important since the neural tube forms very early in pregnancy, even before a woman may be aware that she is pregnant. An Etiology Research Conference on Spina Bifida was co-sponsored by the NICHD in December, 1989, which brought together a multidisciplinary panel of experts to develop a research agenda to identify the causes of spina bifida. The group concluded that though multivitamin supplementation may indeed reduce the prevalence of this defect, the intake of multivitamins may not be the only factor that reduces the incidence of neural tube defects. Rather, it may reflect a life-style associated with multivitamin intake and a concern for the individual health status. The group was cautious about endorsing universal vitamin supplementation, since the benefits still require proof in a randomized clinical trial. Such trials are currently underway in Great Britain and in Hungary, and the Centers for Disease Control is currently planning a pilot study in China. A final answer to this question must await the results of the current trials and most importantly requires examination of the role of folic acid metabolism during normal development in animal models.

Mr. Conte. Can you give us an overview on your efforts to improve maternal nutrition?

Dr. Alexander. The NICHD has funded research aimed at improving maternal nutrition ever since the Institute was founded in 1963. During this period of time, the NICHD has provided the scientific underpinnings that have established the nutrient requirements of pregnant women, including their needs for carbohydrate and protein, as well as their requirements for vitamin, mineral, and trace elements. The NICHD is currently funding studies of the placental transport of these nutrients in order to understand more about fetal growth under various conditions of maternal nutrient supply.

To address the important issue of maternal nutrition in a systematic way, the NICHD supports a research centers program devoted to understanding more about nutrient needs during pregnancy and how to prevent the birth of nutritionally-deprived infants who are at risk of perinatal mortality. Five Perinatal Emphasis Research Centers are exploiting the latest advances in stable isotope and mass spectrographic technology to elucidate the complex problems involved in maternal-fetal nutritional health. These Centers and two other grant projects are devoted to understanding

fetal nutrient supply in a variety of maternal nutritional states, including low and high nutrient intake, obesity and diabetes mellitus.

At present 6.9 percent of all babies born in the United States weigh less than 2,500 grams at birth and are termed low birth weight (LBW) infants. As many as one-half of these LBW infants are infants whose fetal growth has been retarded. Studies funded by the NICHD have shown that intrauterine growth retardation (IUGR) frequently involves impaired maternal nutrition. Maternal and fetal nutrient therapy promises to improve birth weight and subsequent outcome for a significant portion of cases of IUGR.

Over the past 10 years the NICHD has supported a major study in a sheep model of fetal nutritional therapy for intrauterine growth retardation. This project has shown that intragastric or intravenous infusion of nutrients to the fetus will prevent intrauterine growth retardation. Studies are currently under way attemptirg to correct pre-existing intrauterine growth retardation with fetal nutrient therapy and to ascertain the efficacy of various nutrients alone and in combination in reversing the condition before birth. This research holds out the promise of transferring techniques of fetal nutrient therapy to humans who develop IUGR.

Ultimately more important than intrauterine nutritional therapy will be prevention of low birth weight by improving maternal nutrient status. Low birth weight is a particularly important problem among the socioeconomically disadvantaged urban black population. Analysis of national data on the incidence of low birth weight discloses that 12.5 percent of black babies are born weighing 2,500 grams or less versus 5.7 percent of white babies.

A major effort is now under way, in a sample of 600 pregnant women in Washington, D.C., that is designed to correlate maternal nutritional factors with pregnancy outcome. An intervention study will then be undertaken that is designed to reduce the incidence of low birth weight in this population. Preliminary analyses of data on nutrient intakes reveal that one-quarter of the subjects had intakes below 70 percent of the recommended daily allowance (RDA) for carbohydrate, protein, vitamin C, thiamin, riboflavin, and niacin. Dietary intakes of vitamin B6, folacin, magnesium, and zinc were even worse. Perhaps most importantly, nearly one-fifth of the mothers failed to gain 21 pounds during pregnancy, the minimum amount recommended by the American College of Obstetricians and Gynecologists. These investigators also found that low maternal weight gain and low intakes of vitamins A, B6, folacin, and zinc were most predictive of low infant birth weight.

Recently, NICHD staff examined the issue of the effect of maternal nutritional supplementation with multivitamins or folate-containing supplements during pregnancy on the incidence of neural tube defects in over 1,600 women. This study showed that vitamin supplementation during pregnancy does not affect the incidence of neural tube defects.

In order to devise optimal nutrient intake for pregnant women, it is necessary to learn more about maternal nutritional status. With this in mind, the NICHD recently issued a Request for

Applications encouraging scientists to develop new functional tests of nutritional status in pregnant women.

The NICHD is currently developing a new five-year plan for nutrition research, which prominently features maternal-fetal nutrition. New directions in research on maternal nutrition emphasized in this plan include:

1) the development of safe, minimally invasive methods for studying fetal growth and development and its control by nutritional factors;

2) the effect of specific nutrients before, during, and after pregnancy on the health of the pregnant woman, fetus, lactating woman, and infant;

3) the use of the methods of molecular biology to investigate the regulation of fetal growth and metabolism; and

4) intensive studies of the placenta as an organ of nutrient transport.

BIRTH DEFECTS

Mr. Conte. Doctor, can you give us an overall picture on what the best strategy would be to reduce birth defects to the lowest possible rate?

Dr. Alexander. Birth defects result from biological anomalies occurring during the development of the individual. The best overall strategy for reducing birth defects to the lowest possible rate is to increase our understanding of the biology of the developing human. As a result of recent methodological advances, there has been an explosion of information about the molecular control of developmental processes in many animal species. This information is rapidly being applied to mammalian development allowing us to produce animal models which will mimic specific birth defects and to identify the processes which lead to these abnormalities. Once we understand the mechanisms by which individual birth defects occur, we can then devise appropriate strategies for eliminating them.

Mr. Conte. Do you think it is possible to ever achieve this level?

Dr. Alexander. Birth defects can be reduced to the lowest possible level, but this will require an increased effort to understand the biological mechanisms which cause them. This can be attained by emphasizing basic research in developmental biology and placing greater emphasis on the health of women of childbearing ages.

ERYTHROBLASTOSIS FETALIS

Mr. Conte. Doctor, what is erythroblastosis fetalis?

Dr. Alexander. Erythroblastosis fetalis is the destruction of fetal red blood cells (hemolysis) found in some newborns. This

disease can have one of several causes. During the first week of life, a high number of newborn infants have a jaundiced appearance, which is caused by an increase in serum bilirubin. This pigment derives from the hemoglobin of red blood cells. In the newborn, bilirubin is not eliminated efficiently as the needed mechanism is not totally functional. There are various degrees of jaundice, from physiologic levels to a pathologic process associated with severe neurologic sequelae. An increased hemolysis had been observed in cases of fetal-maternal blood group incompatibility (Rh, ABO). This entity is less frequent since the introduction of the use of Rh immune globulin to prevent maternal sensitization. In the treatment and prevention of severe complications, other therapies have and are being used such as exchange transfusion and phototherapy, both of which dispose of the excess of bilirubin after it has already been formed.

Mr. Conte. What research is being done to prevent this disorder?

Dr. Alexander. Over the years, the NICHD has supported the studies that developed and evaluated these treatments. Recently, another therapy has been proposed to treat hyperbilirubinemia before the bilirubin is formed. The results of initial studies using metalloporphyrins (a breakdown product of bilirubin) are encouraging, and the NICHD is supporting various studies in experimental animals and in humans to determine the safety and efficacy of this new therapy.

CONTRACEPTIVE DEVELOPMENT

Mr. Conte. What are the advantages of new contraceptive methods, such as skin patches and long-term injectables, over methods already on the market and those in use?

Dr. Alexander. Long-acting injectable contraceptives offer extended protection (up to 6 months) following a single injection, are highly efficacious (at least as effective as oral contraceptives), and relieve the user of the need to remember to take pills or to use barrier methods. This method of contraception essentially eliminates "patient failure." Unlike injectables, skin patches are applied by the patient at daily or several day intervals. They provide a constant release of contraceptive steroids thus eliminating the peak blood levels following oral or intramuscular administration. Both methods eliminate the problems encountered in absorption of pills from the gastrointestinal tract and the need for orally active steroids.

Mr. Conte. Where do things stand concerning your research efforts in contraceptives?

Dr. Alexander. The Institute is currently supporting clinical trials involving new drugs and devices, including drug delivery systems, disposable diaphragms, and new spermicidal agents which may be attractive to a wide segment of the U.S. population. At the preclinical or laboratory level, we are also pursuing synthesis and testing of new drugs, development of new barrier methods, new methods of drug delivery, newer and safer condoms, and the exploration of antifertility vaccines.

Mr. Conte. In your professional opinion, how much should we be spending in this area, compared to your FY 91 budget request?

Dr. Alexander. Our FY 1991 budget request contains 21.4 million dollars for research programs most closely related to contraceptive development. This figure includes support for contraceptive development, assessment of the medical effects of contraceptive methods now in use, basic science programs directly related to fertility regulation, and behavioral science studies of factors affecting the use of contraception. Inasmuch as this figure has fluctuated little during the past decade while inflation has nearly doubled the cost of research, it would require an addition of approximately 20 million dollars to restore these programs to the level of activity observed ten years ago. The additional funds would enable us to explore more leads for new contraceptives and to hasten progress toward improved methods already under study.

Mr. Conte. How might better research contribute to the prevention of AIDS?

Dr. Alexander. Research targeted at improving barrier methods and the anti-viral properties of spermicides would contribute to the prevention of AIDS.

POLYMERASE CHAIN REACTION (PCR)

Mr. Conte. How will the PCR reaction process contribute to research at your Institute?

Dr. Alexander. The polymerase chain reaction (PCR) is one of the most significant technical advances in molecular genetics in the past decade. PCR makes it possible to amplify specific DNA sequences more than a millionfold in only the few hours needed to complete the automated procedure. It is potentially useful in any situation that requires the examination of DNA. The procedure will determine whether a given DNA sequence exists in a given clinical specimen. PCR is useful in providing a rapid diagnosis, in studying the pathogenesis of disease because of its ability to detect specific DNA sequences that can be correlated with defined pathologic conditions. Some of the genetic conditions for which PCR could facilitate rapid diagnosis include phenylketonuria, sickle cell anemia, insulin-gene mutation in diabetes mellitus, cystic fibrosis, hemophilia, Duchenne muscular dystrophy, Lesch-Nyhan syndrome and Huntington's disease.

INFANT MORTALITY

Mr. Conte. Doctor, as you know, infant mortality is a complex problem involving multitudes of risk factors. Minority populations are especially hard hit by infant mortality -- Secretary Sullivan has made it a top priority for him. What new initiatives will you be undertaking to tackle infant mortality?

Dr. Alexander. In FY 1991, the NICHD anticipates launching several new initiatives in infant mortality research including: new studies of the impact on infants of crack cocaine use by pregnant women; establishment of a network of clinical sites to study the

maturation of cardiorespiratory control during the critical period of infants at risk for Sudden Infant Death Syndrome (SIDS); the development of animal models that test specific hypotheses regarding the cause of SIDS and that can be used for preclinical studies of methods of prevention; SIDS studies to develop the ability to assess human fetal breathing; investigations of new animal models for human birth defects including neural tube defects; clinical trials of aspirin and calcium supplementation to prevent pre-eclampsia; development with the American College of Obstetricians and Gynecologists of the Smoking Trial of Pregnancy (STOP) program to help pregnant women to stop smoking; and the new NICHD Child Health Research Centers that will focus on specific areas of priority in pediatric research, including infant mortality.

PEDIATRIC AIDS

Mr. Stokes. In your professional opinion, are we doing enough in the area of pediatric AIDS? What resources would be needed to meet the needs in this area?

Dr. Alexander. In my professional judgment, we could be doing more in the areas of pediatric, maternal, and adolescent AIDS. There are two areas which must be addressed if this scourge of children and mothers (especially minority and poor mothers and children) is to be addressed adequately.

First, we must expand significantly the clinical trials that will determine how to treat and how to prevent infection in children. We must determine how to treat the infected child who has serious and life-threatening medical problems as well as how to treat the infected pregnant woman so that she does not pass her infection on to her child. To conduct the highest priority research in this area, NICHD would require $25 million annually.

Second, we must increase our basic knowledge about the effect of HIV on infected children as well as infected pregnant women. There are a number of key questions crucial to our understanding of this virus which must be answered if therapeutic research is to proceed in a timely and efficient fashion. An additional $30 million for NICHD for basic biological and biobehavioral research is needed for a better understanding of this virus in children and mothers.

THE AMERICAN TEENAGE STUDY

Mr. Stokes. Last year, we learned that NICHD planned to undertake a survey of adolescent sexual behaviors, knowledge, and attitudes. I understand that the award of this grant was delayed by the Department. How would the information gained help in the AIDS effort?

Dr. Alexander. The American Teenage Study will provide information crucial to understanding how and why adolescents put themselves at risk of AIDS and other sexually transmitted diseases. The study will provide national estimates of behaviors that contribute to risk, as well as information about the sexual networks in adolescent populations that provide pathways for HIV transmission into and within the population. Perhaps most importantly, the study will yield significant scientific advances in understanding the determinants of adolescent risk behaviors. Building on more than two decades of research, the study will examine adolescent behavior in the contexts in which it occurs: in the context of family and parental influence, the school environment and the peer friendship networks, the neighborhood and larger community, as well as in the context of the adolescent's own characteristics, values and aspirations. With its innovative design and large sample size, the study will provide the opportunity to critically examine and test a broad range of hypotheses that have been advanced to explain adolescent risk-taking behaviors. The data set resulting from the study is expected to provide a resource for researchers for years to come. Results will help to inform the design and targeting of effective intervention programs.

Mr. Stokes. Have the Department's concerns been addressed? Will this survey be conducted?

Dr. Alexander. The proposed grant is currently under review in the Office of the Assistant Secretary for Health. We expect any concerns that may be raised during the course of this review to be resolved in time to award the grant this fiscal year. NIH review of the proposed study was completed during the summer of 1989, and consisted of a scientific peer review and site visit, policy review by the NICHD advisory council, and fiscal review by business management staff.

MINORITY EMPLOYMENT

Mr. Stokes. How many minorities are employed by your Institute in grades GM/GS 14 and above? What percentage of the total number of employees in these categories does this figure represent?

Dr. Alexander. There are nineteen (19) minority employees in the NICHD in grades GM/GS-14 and above, or equivalent positions. These represent 17 percent of all employees in these categories.

CONTRACEPTIVE DEVELOPMENT

Mr. Stokes. You told us that NICHD-supported scientists are completing a Phase 2 clinical study of a polyvinyl sponge containing a spermicide. When will these trials be over?

Dr. Alexander. The phase II study of the polyvinyl sponge has been completed. The data indicate effectiveness comparable to that of the cervical cap and diaphragm.

Mr. Stokes. Is this product different than the commercial product now available? If so, when might the new product be available?

Dr. Alexander. The currently available Today Sponge is composed of polyurethane material and is impregnated with nonoxynol-9, while the present sponge is made of polyvinyl and impregnated with benzalkonium chloride.

Although the polyvinyl sponge is available in France and Switzerland, the manufacturers have shown no real enthusiasm to get their product on the U.S. market, which is in contrast to their initial reactions demonstrated at the beginning of the study. The timing, then, is indefinite.

INFANT MORTALITY

Mr. Stokes. The Public Health Service goal for infant mortality in 1990 was 9 deaths per 1,000. You stated that in FY 1988, the rate was 9.9, which is the lowest level ever recorded, but short of the goal. How long will it take us to reach the goal of 9 deaths per 1,000 live births?

Dr. Alexander. Trend line data for the years 1981 through 1987 suggest that we could reach the rate of 9 by 1991. However, since the critical data needed to update the projections are still

provisional, it is extremely difficult to project four or five years ahead with much certainty. Our best guess is that we will reach the goal of 9 deaths per 1,000 live births by 1992 or 1993.

Mr. Stokes. What has prevented us from reaching this goal -- resources or scientific knowledge or something else?

Dr. Alexander. Possible explanations for the recent slowed rate of progress in achieving the goal of 9 deaths per 1,000 live births include changes in maternal characteristics which may increase the proportion of women entering pregnancy at high risk for poor pregnancy outcome such as use of alcohol, tobacco, and drugs such as cocaine, a high rate of unintended pregnancy, and also possible approaching maximum benefit from advances in neonatal intensive care. According to data prepared by the National Center for Health Statistics, deaths of infants born weighing less than 750 grams contribute almost 25 percent of all infant deaths. In order to impact successfully on this large share of infant mortality, very early maternal risk assessment and intervention strategies will be needed.

Mr. Stokes. So that we might have the most recent figures for the record, what is the infant mortality rate among blacks?

Dr. Alexander. The rate is 17.86 per thousand (1987).

BIRTH DEFECTS

Mr. Stokes. Birth defects are still the leading cause of infant mortality. What proportion of infant deaths does this represent?

Dr. Alexander. The Centers for Disease Control has calculated that, of all infant deaths occurring in 1986, birth defects were the underlying or contributing cause in 23.3 percent of infants.

Mr. Stokes. What is your realistic assessment of the likelihood that new research can reduce this tragic number?

Dr. Alexander. Advances in the biomedical sciences are undergoing revolutionary changes which will have direct impact on clinical health problems. In order to reduce the prevalence of birth defects, we must first understand their underlying biological causes. Available technologies now allow us to investigate the biological mechanisms which cause birth defects. Two recent advances are particularly important. Both allow us to develop appropriate animal models for human congenital defects. The first enhances our ability to target gene mutations we wish to produce so that specific changes in genes can be designed. The second allows us to make transgenic animals using embryonic stem cells whose genes have been experimentally altered. Such animal models will provide powerful tools for examining the genetic and epigenetic factors important for normal development.

RESEARCH PRIORITIES

Mr. Early. Doctor, in you opening statement, you say "The broad mission of the Institute and the relevance of its mission to some of the most critical public health problems of our time are reflected in the fact that NICHD research addresses eight of the ten 1992 Public Health Service priorities...". What are these eight priorities?

Dr. Alexander. These eight priorities include infant mortality, AIDS, strengthening the family, drug and alcohol abuse, improving minority health, enhancing health promotion and disease prevention, environmental and occupational health, and maintaining research capacity.

Mr. Early. How effectively do you think you can address these critical health problems with only a 4.2% increase in your budget?

Dr. Alexander. The FY 1991 NICHD President's Budget of $461,473,000 will support a wide range of continuing programs and initiatives in research for mothers and children and in population research. It will be effective because, as in prior years, we will fund only the very best research, making sure that all the research programs of the Institute will be as efficient as possible.

INFANT MORTALITY

Mr. Early. One of the 1990 health objectives was met -- a reduction in neonatal mortality. However, you list ten others where there has been little improvement over the last ten years. Why has there been so little improvement in these areas?

Dr. Alexander. The five areas included in my statement-- the gap between infant mortality rates for blacks and whites; the proportion of women receiving prenatal care early in pregnancy; the incidence of low birth weight and very low birth weight among blacks; the proportion of babies born to unmarried women; and AIDS emerging as a leading cause of death among infants and children-- have shown little improvement over the last decade. These have been among our most difficult challenges, in part because the groups most affected by these problems tend to overlap and, in some cases, are virtually identical. These areas have benefitted, however, from our growing research efforts which, while not directly solving these problems, have ruled out some suspected causes and succeeded in more narrowly focusing our efforts on those factors which are likely to provide answers to these challenges in the future.

Mr. Early. What needs to be done to make progress in these areas? Would more resources help?

Dr. Alexander. The Infant Mortality/Low Birth Weight Initiative launched by the NICHD in 1985 has continued to increase research efforts to overcome these perplexing problems. Building on the advances and the momentum achieved to date, it is important to maintain and expand this effort. Armed with renewed determination and a solid scientific foundation, we are confident that progress can be made in these areas. Additional resources would make it possible for us to make progress at a faster pace.

RESEARCH PROJECT GRANTS

Mr. Early. How many new and competing research grants will NICHD be able to fund with the FY 91 budget request?

Dr. Alexander. The NICHD anticipates funding 362 competing research project grants under the FY 1991 President's Budget.

Mr. Early. How does this compare to prior years?

Dr. Alexander. The numbers of competing research project grants funded by NICHD for the past 10 years are:

FY 1991 Estimate	362
FY 1990 Estimate	323
FY 1989	433
FY 1988	450
FY 1987	545
FY 1986	490
FY 1985	469
FY 1984	415
FY 1983	452
FY 1982	439
FY 1981	453

Mr. Early. What research areas will be affected by this decrease?

Dr. Alexander. Funding fewer competing research project grants affects all major programs of the Institute, including research initiatives in low birth weight/infant mortality, birth defects, fertility research, SIDS, mental retardation, pediatric AIDS, teenage pregnancy, and childhood injury prevention.

Mr. Early. What percentage of approved grants would be funded under the FY 91 budget request? How does this compare to FY 90 and FY 89?

Dr. Alexander. In FY 1991, the NICHD estimates funding 22.5 percent of approved grants. In FY 1990, the funding rate is estimated to be 19.8 percent, and in FY 1989, the funding rate was 26.5 percent.

DOWNWARD NEGOTIATIONS

Mr. Early. What will the downward negotiation for competing and non-competing grants be for your Institute, Doctor?

Dr. Alexander. The downward negotiation rates for NICHD under the FY 1991 President's budget are: competing research project grants--12.0 percent; noncompeting research project grants--15.5 percent; research centers--21.6 percent.

Mr. Early. Doctor Alexander, your Institute is faced with another year of significant reductions. What effect will these reductions have on research programs at you Institute? What about the cumulative affect?

Dr. Alexander. Notwithstanding downward negotiations in both competing and noncompeting research project grants in FY 1991, the average cost of both types of grants will increase in FY 1991. Competing RPG's will increase an average of 7.9 percent over FY 1990, and noncompeting, 4.1 percent. The cumulative effect is less dollars available to grantees for research personnel, and the purchase of supplies, services and equipment. The result will be a slower pace of research and fewer opportunities to pursue new research initiatives.

Mr. Early. What program areas have been most affected as a result of being able to make fewer new and competing awards and these substantial downward negotiations?

Dr. Alexander. Research project grants represent a funding mechanism which includes virtually all of the NICHD programs--across a full range of activities in population research and in research for mothers and children. As such, they would all be affected in some way by fewer numbers of new and competing grants and by reductions from downward negotiations.

RESEARCH PROJECT GRANT MECHANISM

Mr. Early. In addition to the "traditional research project grant (RO1)", what other types of activities does your Institute support through the research grant mechanism?

Dr. Alexander. Within the research project grant mechanism, the NICHD funds these types of grants:

PO1 - Research Program Project
RO1 - Research Project (Traditional)
R22 - U.S.-Japan Cooperative Medical Science Program
R29 - First Independent Research Support and Transition (FIRST) Award
R37 - Method to Extend Research in Time (MERIT) Award
R43 - Small Business Innovation Research Grants (SBIR)-Phase I
R44 - Small Business Innovation Research Grants (SBIR)-Phase II
UO1 - Research Project (Cooperative Agreements)

RESEARCH CENTERS

Mr. Early. Please provide for the record a list of the research centers currently supported by NICHD (indicating the type of center and its focus) and the amount of support each receives. Also indicate those centers that will be up for renewal in either FY 90 or FY 91.

Dr. Alexander. The following is a list of research centers currently supported by the NICHD, with an indication if renewal is scheduled for FY 1990 or FY 1991.

RESEARCH CENTERS

Title and Location	FY 1989 Award
Population Research Centers	
Population Studies Center University of Michigan Ann Arbor, MI	$487,070 **
Center for Population and Reproductive Biology Research Vanderbilt University Nashville, TN	577,440
Carolina Population Center University of North Carolina Chapel Hill, NC	461,516 *
Population Research Center University of Texas Austin, TX	422,774 **
Center for Population Research Harvard University Boston, MA	637,852
Center for Population Research and Studies in Reproductive Biology Baylor College of Medicine Houston, TX	936,851
Center for Research in Primate Reproduction University of Pittsburgh Pittsburgh, PA	474,451 **
Center for Research in Reproductive Biology University of Texas Health Science Center San Antonio, TX	391,575
Population Studies Center University of Pennsylvania Philadelphia, PA	341,321
Reproductive Biology in Primates-Center Facilities Medical Research Foundation of Oregon Portland, OR	529,194
Center for the Study of Reproduction University of Michigan Ann Arbor, MI	593,070
Economic Analysis of the Family and Demographic Change National Opinion Research Center Chicago, IL	469,611

The Laboratories for Reproductive Biology University of North Carolina Chapel Hill, NC	413,129	
Center for Population Research University of Wisconsin Madison, WI	1,045,822	
Hopkins Population Center Johns Hopkins University Baltimore, MD	496,042	
Population Research Center Princeton University Princeton, NJ	83,500	
Reproductive Endocrinology Center Core Facilities University of California San Francisco, CA	669,475	
Population Research Center Harbor UCLA Medical Center Torrance, CA	579,443	**
Mode of Action of Reproductive Hormones Mayo Foundation, Rochester Rochester, MN	973,675	**
Control of the Hypothalamic-Hypophyseal-Ovarian System University of California La Jolla, CA	833,074	
NICHD Population Research Center Studies in Reproductive Medicine University of Washington Seattle, WA	790,527	**
Population Research Center Rand Corporation Santa Monica, CA	537,371	*
Specialized Population Research Center The Population Council New York, NY	1,436,588	
Reproductive Biochemistry and Medicine Columbia University New York, NY	1,373,013	

Mental Retardation Research Centers

Research in Mental Retardation and Child Development University of Washington Seattle, WA	985,725	

Support for Mental Retardation Research Center Yeshiva University New York, NY	1,234,111	*
Program for a Research Center in Mental Retardation University of Kansas Lawrence, KS	770,861	*
Child Development and Mental Retardation University of North Carolina Chapel Hill, NC	797,522	
NICHD Mental Retardation Research Core Grant University of Colorado Denver, CO	426,244	
Research in Mental Retardation E. K. Shriver Center for Mental Retardation, Inc. Waltham, MA	664,909	*
Mental Retardation Research Center University of California Los Angeles, CA	1,149,883	*
Mental Retardation Research Program Children's Hospital Corporation Boston, MA	815,146	**
Wisconsin Center on Mental Retardation - Core Support University of Wisconsin Madison, WI	906,942	**
Core Grant for Mental Retardation University of Chicago Chicago, IL	252,958	
NICHD Mental Retardation Research Center Core Grant Kennedy Institute for Handicapped Children Baltimore, MD	625,467	
Baylor Mental Retardation Research Center Baylor College of Medicine Houston, TX	5,569,256	
Mental Retardation and Human Development Research Center Vanderbilt University Nashville, TN	842,582	
Biology of Down Syndrome University of California San Francisco, CA	197,324	

Center for Research on Developmental Disabilities University of Minneapolis-St. Paul Minneapolis, MN	399,506	

Perinatal Emphasis Research Centers

Perinatal Studies of Disorders of Fetal Metabolism Case Western Reserve University Cleveland, OH	794,710	
Initiation of Human Labor: Prevention of Prematurity University of Texas Health Science Center Dallas, TX	926,413	
Diabetes During Pregnancy: Effects on the Offspring Brown University Providence, RI	893,878	**
Fetal Activity/Responses to Hypoxia During Development Columbia University New York, NY	1,379,880	*
Physiology & Pathophysiology of IUGR University of Cincinnati Cincinnati, OH	525,163	*
Intrauterine Fetal Growth and Metabolism University of Colorado Denver, CO	582,658	*

Endocrinology, Nutrition and Growth Center

Nutrition and Chronic Disease Center University of California Berkeley, CA	318,528	**

Learning Disabilities Centers

Center for the Study of Learning and Attention Disorders Yale University New Haven, CT	774,095	
Neurodevelopmental Pathways to Learning Disabilities Kennedy Institute for Handicapped Children Baltimore, MD	1,019,558	
TOTAL, all centers	$33,407,703	

* Renewal in FY 1990
** Renewal in FY 1991

Mr. Early. Will research centers also be subject to downward negotiations? By what amount (percent) will competing centers be cut? Non-competing centers?

Dr. Alexander. Yes, both competing and noncompeting research centers will be subject to downward negotiations of 21.6 percent under the FY 1991 President's Budget.

Mr. Early. What effect will this downward negotiation have on these centers and their research programs?

Dr. Alexander. The relatively high rate of downward negotiation for the Institute's research centers in FY 1991 is a serious concern of NICHD management. The centers that we will fund in FY 1990 will be able to continue making contributions to the research base, but at a slower rate than if they were fully funded.

Mr. Early. Are some of your centers affected more than others by these downward negotiations?

Dr. Alexander. NICHD centers are comprised of both well-established, continuing programs such as those in mental retardation research, and in the population sciences, as well as newer programs in learning disabilities and child health research. All the centers, however, will be negotiated downward at the same rate. Hence, we anticipate that all the programs will experience a similar impact.

Mr. Early. What is the estimated full cost for research centers in FY 91?

Dr. Alexander. The estimated full cost for NICHD research centers (53) in FY 1991 is $47,097,000.

CLINICAL RESEARCH

Mr. Early. Doctor, to what extent does your Institute support clinical research and what programs or mechanisms are used to support such research?

Dr. Alexander. Clinical research projects comprise 28 percent of the NICHD overall budget. This research involves the population sciences, such as reproductive medicine and contraceptive development, and maternal and child health areas such as high risk pregnancy and infancy, mental retardation, and infant day care--as well as all research mechanisms: research project grants, research centers, cooperative agreements, research career programs, research training, research and development contracts, and intramural research.

Mr. Early. Are there any high priority clinical trials which are ready but cannot be initiated because of lack of funds in the FY 91 request? If so, please provide a list of these, along with a brief description and the associated costs, including first year cost.

Dr. Alexander. Yes, there are major clinical trials that cannot begin due to lack of funds. If additional funds become available, it is anticipated that the following trials could be initiated in FY 1991:

1) Phase II Trial of AZT in Newborns Born to HIV-Infected Mothers. First Year Cost: $2,500,000; Total Projected Cost: $7,500,000.

2) Phase II Trial of AZT Administered to HIV-Infected Women in the Third Trimester of Pregnancy. First Year Cost: $3,500,000; Total Projected Cost: $10,500,000.

3) Testing of Disposable Spermicide Releasing Barrier Devices. First Year Cost: $350,000; Total Projected Cost: $1,100,000.

4) Event Recording of Apnea & Bradycardia in High-Risk Infants. First Year Cost: $750,000; Total Projected Cost: $2,000,000.

5) Cooperative Multi-Center Reproductive Medicine Network. First Year Cost: $2,000,000; Total Projected Cost: $8,000,000.

6) Calcium Supplementation in the Prevention of Pregnancy-Induced Hypertension and Preterm Birth. First Year Cost: $300,000; Total Projected Cost: $4,300,000.

7) Interventions to Improve African-American Pregnancy Outcomes. First Year Cost: $1,200,000; Total Projected Cost: $6,000,000.

8) Prognostic Clinical Tests for SIDS. First Year Cost: $3,500,000; Total Projected Cost: $18,000,000.

9) Use of Ambulatory Tocodynamometry to Prevent Preterm Birth. First Year Cost: $2,500,000; Total Projected Cost: $8,000,000.

10) Collaborative Multicenter Clinical Trial of Hyperventilation v. Minimal Ventilation in Patients with Primary Pulmonary Hypertension of Newborn. First Year Cost: $1,500,000; Total Projected Cost: $3,000,000.

11) Iron Deficiency Anemia and Infant Behavior: A Prevention Trial. First Year Cost: $220,000; Total Projected Cost: $660,000.

RESEARCH CAREER PROGRAM

Mr. Early. Will you bring us up to date on the Institute's research career program? I see that in FY 90 there is an increase of 15 RCP awards. On what areas have you focused?

Dr. Alexander. The NICHD research career program is represented in both of the Institute's major research activities--72 percent in research for mothers and children, and 28 percent in population research. In FY 1989, a total of $6.6 million was spent on 98 research career awards. The program provides salary support for basic scientists, mostly with Ph.D's, as well as for physicians engaged in clinical research. The focus for the additional awards in FY 1990 will be for clinicians, the physician scientists and the clinical investigators, with the objective of filling a vital need for developing research personnel in the areas of pediatrics and obstetrics/gynecology.

Mr. Early. Doctor, has there been any improvement in the supply of research scientists in obstetrics, peri- and neonatology, and

pediatrics? What is the current assessment of the need in these areas?

Dr. Alexander. The NICHD is currently supporting two innovative career development grants addressing the need for an increased number of research scientists in obstetrics, peri- and neonatology, and pediatrics. These are the Pediatric Physician Scientist Program and the Reproductive Scientist Program. Physicians are selected for these programs after they complete their residency in pediatrics or in obstetrics and gynecology. The awardees are sponsored by an institution for a five-year period. After completing two or three years of intensive basic research preparation in a distinguished laboratory, the developing research scientists join the faculty of the sponsoring institution, with the guarantee of 75 percent protected time for research. These programs are in their fourth and third year, respectively, and an exciting group of new physician scientists is acquiring the modern tools of basic research to be applied to clinical problems. While these activities will improve our supply of such researchers, the degree of improvement remains below the replacement needs of the research community that have been projected for the next decade. It is clear that our effort to promote physician-scientist research career development must be continued as a priority effort.

PEDIATRIC AIDS

Mr. Early. I understand that NICHD is now funding six major pediatric AIDS centers. What mechanism is being used to fund these centers?

Dr. Alexander. One of the Institute's major efforts in pediatric AIDS involves the funding of six medical centers, through the research project grant mechanism, to develop improved methods of early diagnosis of HIV in infants.

Mr. Early. Do these centers have a particular area of research emphasis?

Dr. Alexander. These six grantees are focusing their research efforts on the development of improved methods of early diagnosis of HIV in infants.

Mr. Early. Where are these centers located?

Dr. Alexander. The six grantees are located in Miami, Florida; Los Angeles, California; Houston, Texas; Chapel Hill, North Carolina; New York, New York; and Manhasset, New York.

Mr. Early. For the record, please provide a list of these centers and the amount of the grant award.

Dr. Alexander. The six grantee institutions and the amounts awarded in FY 1990 are listed below:

University of Miami School of Medicine Miami, Florida	$526,078
University of California at Los Angeles Los Angeles, California	425,000 Estimate
Baylor College of Medicine Houston, Texas	715,924
University of North Carolina at Chapel Hill Chapel Hill, North Carolina	194,063
New York University Medical Center New York, New York	336,751
North Shore University Hospital Manhasset, New York	678,234

Mr. Early. Does the FY 91 request include adequate support for these centers in the second year?

Dr. Alexander. In FY 1991, these grants will be funded as noncompeting continuation awards with a downward negotiation rate of 15.5 percent.

Mr. Early. How would you assess the adequacy of current access to state-of-the-art research and care for infants and children with AIDS or HIV?

Dr. Alexander. An important advance in this area is that the National Institute of Child Health and Human Development and the National Institute of Allergy and Infectious Disease have joined two heretofore separate clinical trials groups into one unified entity. This unified group will jointly develop and conduct clinical trials in infants, children, adolescents, pregnant women, and mothers. It is important to understand that participation in clinical trials in this group not only entails access to drugs which are the most promising in the treatment and prevention of this disease. Access to clinical trials research is also access to state-of-the-art care. Most patients in the clinical trials group see access to clinical trials as hope for a longer and better life for themselves and their children. Right now, this clinical trials group has the opportunity to give access to clinical trials to the majority of HIV-infected pregnant women and children in the United States. This is a monumental achievement.

Mr. Early. What treatments are available for infants and children who have AIDS or are HIV positive?

Dr. Alexander. Right now, there are no drugs which are licensed by the FDA to treat HIV infection including AIDS in children. Currently, children judged by their physician as requiring AZT and

meeting certain specified criteria may receive AZT as an investigational new drug.

CONTRACEPTIVE DEVELOPMENT

Mr. Early. The budget justification speaks of efforts being made to move forward with the development of improved methods of contraception. However, Doctor, there have been no new contraceptives developed in the U.S. since "The Pill", and that was, what, 30 years ago? Why hasn't there been any progress?

Dr. Alexander. Substantial progress in new contraceptive technology has been made during the last 30 years including modified oral contraceptive regimens and reduced dosages, more potent progestational agents with reduced side effects, better intrauterine devices and the introduction of the vaginal contraceptive sponge. Projects in the "pipeline" include long-acting injectables, new generation implants, dermal patches and methods for the male. Contraceptive research and development by the private sector all but disappeared during the later half of this period and government funding has remained almost constant. Costs of research have risen substantially during the last 20 years due to inflation, markedly increased liability insurance and, more recently, by new rules regulating research with animals (Animal Welfare Act of 1985). It is estimated that implementation of the new animal standards alone will impose a direct burden in excess of $1 billion to research institutions.

Mr. Early. The justification discusses every effort being made to move forward "within available resources". If there were more resources, would there be more progress, Doctor?

Dr. Alexander. Funds available for contraceptive research and development and closely related programs have remained almost static over the last ten years while inflation and other factors have doubled the cost of undertaking this work. Thus, if resources were to double, we could restore the level of effort to that observed ten years ago.

CLINICAL RESEARCH IN REPRODUCTIVE HEALTH

Mr. Early. Doctor, is there an inpatient reproductive health research unit at the Clinical Center? Are there clinical beds dedicated to this area of research? If not, why not?

Dr. Alexander. There is a Unit on Reproductive Endocrinology within our Developmental Endocrinology Branch. This unit carries out research on disorders of men and women which affect their reproductive health. When these studies require an inpatient admission, beds are allocated for this purpose on the 10W Nursing Unit in the Clinical Center. Current clinical research protocols in this area include Premature Ovarian Failure; Endometriosis; Male Infertility; Female Infertility, and Polyglandular Disorders.

SEXUALLY TRANSMITTED DISEASES

Mr. Early. What are your program plans for FY 90 and FY 91 in the area of STD research (exclusive of AIDS)? How much has been allocated for STD research in each of these years?

Dr. Alexander. In the summer of 1990, a prospective trial of barrier methods will be initiated for the study of gonorrhea, chlamydia, and herpes. These organisms were chosen because they have high incidence rates, similar transmission modes, and they are public health problems. The intervention strategy will encourage the proper and consistent use of condoms, spermicides, sponge, and possibly some barriers not presently available to the American population (e.g., female condom).

Other studies planned include: (1) studies to ascertain and quantify the reduction in the risk of bacterial, chlamydia, and viral sexually transmitted diseases and pelvic inflammatory disease (PID) among women who use barrier methods of contraception; (2) investigation of the contraceptive effectiveness of a regimen of two barrier contraceptive methods compared to the use of either one alone; (3) studies to determine what are maximally inhibitory spermicides against viral STD pathogens, including hepatitis; and (4) Barrier Contraceptive Primary Prevention Trials aimed at assisting young men and women to increase their measure of personal protection against sexually transmitted diseases, which will include education in the use of condoms, spermicides, and other personal hygiene activities; (5) research on the absorption and hepatic toxicity of the active compounds in spermicidal foams, creams, and jellies; (6) investigation of the effectiveness and safety of prophylactic antibiotics as a means of reducing the incidence of PID in users of certain IUDs; and (7) investigation of the role of spermicides in reducing the risk of papilloma virus infection and the relationship to precancerous cervical changes. In FY 1990 and FY 1991, the NICHD has allocated $5.9 million and $6.1 million, respectively, for research on sexually transmitted diseases, exclusive of AIDS.

Mr. Early. What progress can you report in this area since last year?

Dr. Alexander. The NICHD supports a large research program on the role of contraceptives in preventing the spread of sexually transmitted diseases. Last year, a major laboratory program designed to evaluate the suitability of using condoms and spermicides for STD prevention was completed. A condom testing program was conducted to determine if prophylactics purchased in stores meet industry standards for quality and are sufficient barriers against STDs. The results show that the high quality of the current supply of condoms on the American market should provide a substantial degree of protection against STDs.

Spermicides used in conjunction with condoms were found to provide additional protection against infection with STDs in the event of condom damage.

Also completed last year as a spermicide testing program that compared the inhibitory effects of 6 spermicides with regard to 9

STDs. The STDs included gonorrhea, syphilis, chlamydia, and herpes simplex II. The 6 spermicides were available commercially, although only two, nonoxynol-9 and octoxynol, are marketed in the United States. The results of the tests suggested that all of the spermicides are effective against some of the common STDs. Oxtoxynol and benzalkonium chloride appeared to have the best overall effectiveness against a spectrum of STD agents.

Mr. Early. What did you originally request for STD research?

Dr. Alexander. The amount requested for research on sexually transmitted diseases in the NICHD budget originally submitted to NIH was $8 million.

ATHEROSCLEROSIS IN ADOLESCENCE

Mr. Early. I understand that evidence is accumulating that atherosclerosis leading to coronary artery disease begins in adolescence or even childhood. What can you tell us about this?

Dr. Alexander. Coronary artery disease is the leading cause of death in the American adult population and is responsible for more than 500,000 deaths per year. It is now clear that the arterial lesions of atherosclerosis have their origin in childhood. Fatty streaks are the earliest lesions of the atherosclerotic process and many of them progress to become clinically significant deposits that narrow the channel of coronary arteries. Fatty streaks develop in early childhood and are almost universal in the aortas of children of both sexes regardless of ethnic background; moreover, fatty streaks have been found in the coronary arteries of some adolescents during the second decade of life.

Recently serum lipid levels have been directly related to the extent of early arterial lesions of atherosclerosis in adolescents. Investigators in the Bogalusa Heart Study have assessed the relationship of serum lipids to early atherosclerotic lesions in the aorta and coronaries of 35 study subjects, 7 to 24 years of age, whose mean age at death was 18 years. They found that aortic fatty streaks correlated strongly with levels of both total and low-density lipoprotein cholesterol.

Mr. Early. How is NICHD addressing this problem?

Dr. Alexander. Early detection of this process will pave the way to preventing the ravages of this serious disorder later in life. The NICHD is attacking this important problem by supporting an ambitious study of lipids of several hundred adolescents from coronary disease-prone families at the University of Cincinnati. The NICHD-supported investigators have shown that adolescent boys from families prone to coronary artery disease have high levels of three serum factors. Men who have heart attacks before age 55 also have high levels of these serum factors which can now serve as markers in adolescence for increased risk of coronary artery disease later in life. Development of such metabolic markers is critical to mounting an intensive intervention effort in childhood and adolescence aimed at preventing coronary atherosclerosis.

The NICHD is also supporting a large prospective study in over 900 individuals of the natural history of fat, blood lipids, and health. The study has shown that adolescent boys with excessive accumulation of abdominal fat also have decreased levels of high density lipoprotein (HDL) cholesterol which protects against the development of coronary atherosclerosis. These results point to adolescent abdominal obesity as an indicator of cardiovascular risk in adulthood.

Mr. Early. Are there any joint efforts with the NHLBI?

Dr. Alexander. Staff of the NICHD have worked with staff of the NHLBI to assemble the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. This panel will produce a final report in June 1990. This report will make recommendations regarding screening and management of children and adolescents with elevated levels of cholesterol and other serum lipids.

The NICHD Five-Year Plan for Nutrition Research contains a key chapter on this topic which notes that safe and effective interventions in children have not been worked out, and that longitudinal studies would require follow-up of an impractical duration. Since the safety and efficacy of dietary interventions in reducing elevated low density lipoprotein levels in children are currently being investigated in clinical trials sponsored by the NHLBI, the resources of the NICHD might be used most effectively in this area by supporting studies of the eating behavior of children and its influence on plasma lipids, as well as of the mechanisms by which early nutrient behavior affects lipid metabolism.

Activities in which the NICHD and the NHLBI could collaborate include studies of dietary intake of children; studies of how nutrient intake influences cholesterol metabolism in children; how this influence varies with race, sex, and age; developing a non-invasive method for measuring the progression of arterial fatty streaks to the dangerous intraarterial lesions of coronary atherosclerosis; and developing epidemiologic techniques which would permit the correlation of genetic or metabolic markers in children with a familial tendency to premature cardiovascular disease.

USE OF ADDITIONAL FUNDS

Mr. Early. If an increase over the FY 91 request is provided, how would you use these additional funds?

Dr. Alexander. The first priority for the use of additional NICHD FY 1991 budget authority would be to lower the downward negotiations in both research project grants and centers. The Institute continues to place the utmost importance on investigator-initiated research project grants, and virtually all of the research programs of the Institute depend on this funding mechanism. Still further resources would be used to support more competing projects, to approach a goal of funding 40 percent of approved research project grant applications. The NICHD would support more research centers, adding two centers each in mental retardation research and in population research, and three additional child health research centers, to approach the minimal level originally envisioned for the new child health research centers program. Funding would be

provided for additional research career awards, with emphasis on the physician scientist and clinical investigator awards; for expansion of the Institute's cooperative clinical research networks, including full-funding of the 10 units of the infant day care research networks, as well as initiation of clinical trials within the multi-center reproductive medicine network. In addition, funds would be provided to begin a cooperative clinical network for studies related to Sudden Infant Death Syndrome, and there would be increases for minority biomedical research support grants. Research Training is another high priority of the Institute. We would use additional funds in FY 1991 to support more trainees, thereby giving increased opportunities for research training across a broad range of biomedical and behavioral sciences. Many important research areas of the NICHD depend on R & D Contracts as the mechanism for program support. Most prominent are the areas of AIDS research, clinical trials, and contraceptive research. Additional funds would be used for expansion of research efforts in pediatric AIDS, drug abuse in pregnancy, contraceptive development and evaluation, SIDS, infant mortality, teenage pregnancy and vaccine development. Finally, there would be increases provided to the NICHD Intramural Research Program and for Research Management and Support.

RESEARCH INITIATIVES

Mr. Early. Will any significant new research initiatives or opportunities be lost or delayed by lack of funds in the FY 91 budget request? Please provide, for the record, a list of these along with a brief description and the funding requirements associated with each.

Dr. Alexander. The FY 1991 budget request will allow the Institute to fund its highest priority initiatives, but at less than predicted full costs. Scientific opportunities that are unplanned happen frequently. The FY 1991 level provides less flexibility to take advantage of these kinds of opportunities, however, should essential ideas emerge, we would of course reorient our priorities and support them.

Institute initiatives and opportunities that would be affected by FY 1991 funding levels, along with the additional amounts required to bring them to an estimated full-cost level, include: prevention of low birth weight and infant mortality initiative, $30 million, above a base of $61.4 million; contraceptive development initiative, $34 million, above a base of $21.4 million; AIDS research $25 million; establishment of two additional mental retardation research centers, $1.8 million; two additional population centers, $1.8 million; three additional child health research centers $1.2 million; expansion of the reproductive medicine network, $1.0 million; funding of major new clinical trials ready to begin in FY 1991, $18.3 million; continued implementation of the SIDS 5-year plan, $15 million; childhood injury prevention, $2 million; drug abuse in pregnancy, $5 million; increase in intramural research and research management and support, $6 million.

Mr. Early. To what extent will there be major reductions in the scope of ongoing or new initiatives because of the FY 91 funding levels? For the record, please provide a list of these along with a brief description and the amounts associated with each initiative.

Dr. Alexander. The major reductions in the scope of ongoing and new initiatives would be the same as described earlier for the "opportunities that would be lost or delayed by lack of funds." The principal areas are: Prevention of low birth weight and infant mortality, contraceptive development, AIDS, centers for mental retardation, child health research and population research, reproductive medicine networks, major new clinical trials, SIDS, childhood injury prevention, drug abuse in pregnancy, and intramural research and research management and support.

PROFESSIONAL JUDGMENT BUDGET

Mr. Early. Doctor, what is NICHD's professional judgment budget for FY 91? What are the major differences from the request before us?

Dr. Alexander. The professional judgment budget for the NICHD in FY 1991 is $635,306,000. Within the research project grant mechanism, the Professional Judgment budget provides funds to eliminate all downward negotiations as well as to increase the funding rate from 22.5 percent to 40 percent of approved applications. The professional judgment budget includes funds to restore full cost funding to the 53 current research centers, as well as funds to establish two new mental retardation research centers, two new population research centers, and three additional child health research centers. Funds have been provided in the other research mechanism for additional research career awards, which include physician scientists and clinical investigators. Funds have also been provided for expansion of research within the Institute's cooperative clinical research networks. This includes full funding of the 10 units comprising the infant day care network as well as the initiation of clinical trials within the newly established cooperative multi-center reproductive medicine network. In addition, funds have been included to begin a cooperative clinical network for studies related to SIDS. Increases have also been included for minority biomedical research support grants. The FY 1991 Professional Judgment budget provides support for 800 research trainees, 110 more than the FY 1991 President's Budget.

Additional funds have been included in research and development contracts for necessary expansion of the Institute's research efforts in pediatric AIDS, drug abuse in pregnancy, contraceptive development and evaluation, SIDS, infant mortality, teenage pregnancy, and vaccine development. An increase of $4 million has been included for intramural research for expanded efforts in biotechnology, neurobiology, vaccine development, additional staffing requirements, and AIDS prevention research. The additional amount for research management and support will provide funds for additional staff for extramural program management and Institute-sponsored conferences such as on AIDS and learning disabilities.

MENTAL RETARDATION RESEARCH CENTERS

Mr. Early. Would you bring us up to date on the research activities and progress being made in the Mental Retardation Centers program.

Dr. Alexander. A dietary therapy has been developed by an investigator in one of the Mental Retardation Research Centers (MRRC) that normalizes, at least in part, the major biochemical abnormality in a genetic condition called adrenoleukodystrophy (ALD). ALD affects mainly the adrenal cortex, the brain, and testes. While the endocrine deficits can be helped by steroid replacement, the neurological disability cannot be treated and often leads to severe disability and premature death. Although the dietary treatment has not been able to reverse existing neurological deficits, it can prevent the occurrence of neurological impairment when it is initiated before a patient shows clinical symptoms.

Duchenne muscular dystrophy (DMD) is a severe X-linked disorder with about one third of patients exhibiting associated mental retardation. An investigator at the MRRC in Boston cloned the DMD gene and identified the gene product which he and his associates called "dystrophin". This molecule is absent in the muscle of patients with DMD and quantitative measurement of this protein is used in the prenatal and postnatal diagnosis of DMD. In a mouse model for DMD, it was found that immature muscle cells, called myoblasts, injected into muscle can fuse with muscle of the affected animals and supply dystrophin to the afflicted muscle cells. Studies are currently underway to refine and extend this observation in animal models before the feasibility of clinical trials in human subjects can be initiated.

The success of nationwide neonatal screening for phenylketonuria (PKU) created a new problem as PKU women reached childbearing age. Retrospective surveys of untreated maternal PKU revealed that elevated levels of maternal blood phenylalanine is associated with a high incidence of mental retardation, small head size, congenital heart defects and growth retardation. A nationwide project supported by NICHD is testing the efficacy of a low phenylalanine diet in preventing the morbidity associated with maternal PKU. Preliminary results suggest that diet initiation during the first trimester, and preferably prior to conception, reduces the deleterious effects of maternal PKU on reproductive outcome.

CONTRACEPTIVE DEVELOPMENT

Mr. Dwyer. Time magazine recently reported on the numerous contraceptive options available to European men and women versus those available to their American counterparts. In addition, the limited number of effective contraceptive choices has been linked to the high rate of unplanned pregnancies as well as the high rate of surgical sterilization in this country. Why is the United States lagging behind European countries in the development and availability of new contraceptive products?

Dr. Alexander. A number of European pharmaceutical companies are pursuing various contraceptive leads including abortifacients. However, in the United States, only one pharmaceutical company remains in the contraceptive field because of the discouraging regulatory and legal climate. It should be noted in this connection that Europeans are less litigious than Americans. In addition, there are financial considerations involved such as the skyrocketing cost of research, the length of time required for the development of contraceptive agents, and the burden of product liability suits. The Pharmaceutical Manufacturer's Association puts the cost of a new drug entity at around $125 million. Thus, pharmaceutical companies in the U.S. have invested their research dollars in other areas where there is less financial risk and greater potential return.

Mr. Dwyer. When do you believe these devices, such as the implant, will be available in the United States?

Dr. Alexander. Several new contraceptive steroids available in Europe will probably become available following FDA approval within the next five years. However, a number of drugs, including two injectable formulations, have already been rejected by the FDA and the likelihood of their availability is slim. One new contraceptive steroid was approved for use by the FDA late last year, but marketing of this new product (Norgestimate-Ortho) is expected to be delayed due to patent interference. Norplant® has essentially been approved by both the FDA and its Fertility and Maternal Health Drugs Advisory Committee pending receipt of the final NDA. This implant which releases the synthetic progestogen, levonorgestrel, will probably reach the U.S. marketplace later this year.

Mr. Dwyer. Since the Dalkon Shield controversy, there has been a marked decline in the use of intrauterine devices in the United States. It is my understanding that several new and safe IUDs have been developed. Do you believe that IUDs will ever become "popular" again in the United States?

Dr. Alexander. IUDs appeal only to a very small segment of the population and will probably never achieve the popularity of the oral contraceptives. There is a general concern among women regarding the possibility of pelvic inflammatory disease and potential sterility with IUD use.

SEXUALLY TRANSMITTED DISEASES

Mr. Dwyer. The budget justification mentions that NICHD is conducting a contraceptive evaluation program to examine the degree to which barrier contraceptive devices reduce the risk of certain sexually transmitted diseases. What is the status of this evaluation?

Dr. Alexander. The program to evaluate barrier contraceptives for their efficacy in preventing sexually transmitted diseases consists of laboratory testing of spermicidal agents for antimicrobial properties as well as clinical observational studies of the degree to which barriers prevent sexually transmitted diseases in users. The Institute is seeking R&D contract proposals for a clinical observational study of several barrier contraceptive regimens for the prevention of particular sexually transmitted diseases. This study will follow approximately 1000 women, each using one of four regimens (condom, spermicide, condom plus spermicide, or sponge), for the occurrence of gonorrhea, chlamydia, or herpes. Rates of disease among each user group will be compared to rates in women who are not using a barrier contraceptive. This study will start by September 1990.

Laboratory work on spermicides will ascertain the ability of detergents (like Nonoxynol-9) and their delivery vehicles to inactivate several organisms responsible for sexually transmitted diseases. Related investigations will calculate the concentration of spermicide present in the vagina under a variety of assumptions about dilution, and other studies will discern the quality of Nonoxynol-9 as it is stored under various conditions. Further studies will emphasize potential toxicity of spermicidal agents by examining their effects on vaginal epithelial cells, vaginal immune cells, and the protective glycoprotein layer that covers the vagina. The NICHD expects to begin these studies in FY 1991.

PEDIATRIC AIDS

Mr. Dwyer. As you may know, Pediatric AIDS is an enormous problem in New Jersey. Five metropolitan areas in New Jersey are among the top 25 metropolitan areas for reported Pediatric AIDS cases. NICHD is currently investigating intravenous immunoglobulin (IVIG) as an effective deterrent against opportunistic bacterial infections in HIV positive children. How is this research progressing?

Dr. Alexander. This research project was divided into two strata: one with sicker children in it (Group I) and one with less symptomatic children in it (Group II). Group I has closed enrollment because the necessary sample size has been reached. Group II has only to enroll approximately 30 more children and then this stratum will be closed as well. Between the two groups, over 400 children will have been enrolled by the time recruitment ceases. These children are cared for in 28 medical centers around the country including 3 in Puerto Rico. The treatment period in the study extends for two years so, even after enrollment closes, there is a significant period of study still to be completed. However, an outside panel of experts periodically reviews this trial and its

interim data so that the trial can be discontinued if it is demonstrated early that the drug is effective.

This study is the largest therapeutic trial in the world involving HIV-infected children. It has offered access to state-of-the-art care to hundreds of children and, by joining forces with the NIAID-supported pediatric clinical trials group, will continue to offer this to many more infected children and pregnant women.

Mr. Dwyer. Pediatric AIDS is different from its adult counterpart, because the immune system is immature. Aside from typical "childhood diseases," what opportunistic infections are more prevalent in Pediatric AIDS patients?

Dr. Alexander. The principal difference regarding opportunistic infections in adult versus pediatric AIDS patients is that the problem of recurrent serious bacterial infections is much more common in HIV-infected children than in HIV-infected adults. These bacterial infections can be life-threatening to these children. They include sepsis, meningitis, pneumonia, osteomyelitis, septic arthritis, and other deadly infections. Even if these infections do not result in the death of the child, treatment of them is prolonged and always involves hospitalization and intravenous drug therapy, sometimes for weeks at a time. The NICHD trial of the use of intravenous immunoglobulin in these children will answer the question of whether or not these deadly infections can be prevented.

AIDS IN HEMOPHILIAC CHILDREN

Mr. Dwyer. I was pleased to learn that NICHD has become active in studying the effect of HIV infection in hemophiliac children, as nearly 90% of all hemophiliacs are seropositive for AIDS. Do HIV-positive hemophiliacs have unique problems?

Dr. Alexander. Any child with severe hemophilia faces significant physical and emotional challenge throughout life. These children can suffer strokes and hemorrhages into their joints which may result in impaired growth. Because of transfusions, they are exposed to infectious agents which may result in serious diseases involving hospitalization and even chronic problems. Adding HIV infection to this very vulnerable population, unique problems can result. For example, the immune system of children who face exposure to blood-borne infectious agents is under attack. Children whose growth is impaired by damage to the joints because of hemorrhage may have their growth further impaired by their HIV infection. Children who may have suffered strokes may also have central nervous systems further damaged by the direct effects of HIV on the brain.

CHILD HEALTH/MENTAL RETARDATION CENTERS

Mr. Hoyer. I was and continue to be a strong proponent of the Child Health Research Centers which the Chairman generously helped us fund in last year's appropriation. I have also been a strong supporter of research on a form of mental retardation called Rett syndrome which is supported through NICHD mental retardation research centers, and I am very concerned about the possibility that continued downward negotiations are beginning to interfere with good science. Dr. Hugo Moser, one of the investigators leading the research on Rett syndrome, indicated to me that continued increases in funding for Rett syndrome research would not be as productive if we continue to destabilize the core center budgets with these downward negotiations. Of the funds you received in the President's request for FY 1990, how much had you anticipated using for the Child Health Research Centers?

Dr. Alexander. The President's request for FY 1990 included no funds for the Child Health Research Centers.

Mr. Hoyer. How much of the funding above the request had you anticipated using to fund the centers?

Dr. Alexander. The $2 million less sequestration earmarked in the appropriation was provided above the request and will be used for these centers.

REDUCTIONS IN THE FY 1990 BUDGET

Mr. Hoyer. Can you tell the subcommittee the impact of the sequester, the salary cap and any other reductions on the FY 1990 NICHD budget?

Dr. Alexander. The reductions to the FY 1990 budget for NICHD were:

Extramural Salary Cap.....	$ 583,000
Procurement Reduction.....	311,000
Salaries and Expenses Reduction....	612,000
Sequestration.....	6,173,000
Total	$7,679,000

The principal impact of these reductions will be the support of approximately 19 fewer research project grants, spread across all NICHD program areas, and a 3.5 percent increase in the downward negotiation rate on project and center grants. The procurement and salaries/expenses reductions will have a more limited, but nevertheless effective, impact by decreasing the amount of intramural research by NICHD scientists, and the extent of service to grantees by their extramural staff colleagues.

RESEARCH CENTERS

Mr. Hoyer. The new centers, including the learning disability program are important priorities for the Committee and for NICHD, but what would have been the savings if we had initiated one or two fewer centers for FY 90?

Dr. Alexander. Of the $36,914,000 available in FY 1990 for research centers, the NICHD proposes to fund 53 centers with downward negotiations of 17.1 percent. These 53 centers include six new child health research centers and one new learning disability center. If the NICHD had proposed the establishment of only two new child health research centers, the resultant savings could have reduced downward negotiations from 17.1 percent to 14.2 percent.

Mr. Hoyer. What was the rate of downward negotiation in the NICHD centers budget for FY 1987, 1989 and 90?

Dr. Alexander. The rates of downward negotiation in the NICHD center grant awards for these years are: FY 1987--9.5 percent; FY 1989--13.6 percent; FY 1990 estimate--17.1 percent.

Mr. Hoyer. What is the expected rate of downward negotiation for the centers budget for FY 1991 under the President's request?

Dr. Alexander. The proposed downward negotiation rate for NICHD research centers in FY 1991 is 21.6 percent.

Mr. Hoyer. Going back to a question that Mr. Early has asked, I would like a much better understanding of how the "Base" for the centers is defined, as well as how these downward negotiations practically impact the retardation centers?

Dr. Alexander. The base for the NICHD research centers represents the full cost amounts as recommended by our national advisory council, which is often higher than the amounts received the previous year on multi-year awards. The full cost of the average center grant will rise from $840,000 in FY 1990 to $889,000 in FY 1991. Downward negotiations within the mental retardation research centers will affect the hiring of scientists and technical staff, the amount of supplies and equipment that could be purchased, and other support services such as replacing or upgrading old equipment.

Mr. Hoyer. Given additional funds over the request, what priority would you give to reducing the expected level of downward negotiation on the research centers?

Dr. Alexander. Reducing the level of downward negotiation on NICHD research project grants and centers would be the first priority for any additional funds over the Request.

Mr. Hoyer. What was the level of projected center downward negotiations in the budgets submitted to NIH, the OASH, the Secretary, and OMB?

Dr. Alexander. The NICHD budget submitted to NIH provided full-cost funding for all research centers. Since budgets submitted to the OASH and the Secretary are consolidated at the NIH level, and not broken down by Institute, an NICHD figure for downward negotiations was not available. The NICHD budget submitted to the OMB reflected a downward negotiation rate of 24.1 percent for research centers.

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Mr. Hoyer. Could you provide the Committee a projection of the funds required to reduce the downward negotiations to 18%, 15%, 14%, 12% in 91?

Dr. Alexander. The FY 1991 President's Budget provides funding for 53 research centers at $36,914,000 with downward negotiations of 21.6 percent. The table below reflects the amounts required above the President's Budget to reduce the downward negotiations to the levels indicated.

Downward Negotiation Rate	Additional Amount Required
18 percent	$1,706,000
15 percent	3,118,000
14 percent	3,589,000
12 percent	4,531,000

WOMEN AS SUBJECTS IN CLINICAL RESEARCH

Mr. Hoyer. I have become very interested in our ability to include women as subjects in research. Given the areas of NICHD interest could you assess the Institute's record since 1987 in including women in clinical trials or other research?

Dr. Alexander. The NICHD is sensitive to insuring that its research, particularly its clinical trials, include appropriate representation of subjects by gender, race, and other factors. A high percentage of the Institute's research, however, is gender-specific with most of its research subjects being women. For instance, studies of pregnancy, of course, involve only women. Some NICHD studies are necessarily limited to men--the development of male contraceptives, for example, and others seek to insure appropriate representation of both sexes and the relevant race populations. The Institute's record of involving large numbers of women in its research dates back to its founding in 1963.

Mr. Hoyer. Have any grant applications been re-evaluated on the basis of its failure to include an adequate number of women?

Dr. Alexander. Given the nature of NICHD research populations, it would be rare for there to be a need for a grant application to be re-evaluated on the basis of its failure to include an adequate number of women. While we cannot identify such a case, the Institute's sensitivity to this issue makes it possible but unlikely that such a situation has occurred.

SUDDEN INFANT DEATH SYNDROME

Mr. Hoyer. Could you outline any progress in the area of SIDS, including any new information on triggering events, the disproportionate impact on minority children?

Dr. Alexander. Investigation on a large number of specimens, obtained from the NICHD Collaborative Epidemiologic Study, confirmed that SIDS victims are more likely to have pinpoint hemorrhages of the lungs and thymus, and production of blood cells in the liver. However inflammation of the upper airway and congestion of the lungs was not more common in SIDS victims compared to infants dying of

known causes. These findings suggest that SIDS infants may be exposed to chronic lack of oxygen and/or are delayed in their maturation.

We have other evidence that SIDS infants are delayed in their maturation. SIDS infants have difficulty controlling heart rate and breathing early in life. In both waking and active sleep, the magnitudes of three types of heart rate variability was diminished in infants who later died of SIDS compared with infants who survived, and the decreased magnitude was more apparent at specific times of the night.

Quantitative studies of the brains of SIDS victims show that areas of the brain which regulate cardiorespiratory function, such as heart rate variability, appear younger than the actual age of the infant whereas areas of the brain controlling respiratory organs are appropriate for the infants age. Myelination of the brain, a process which is initiated in fetal life and continues throughout infancy, and is necessary for nerve cell communication, is also delayed in SIDS victims.

The NICHD Collaborative SIDS Epidemiologic Study showed that SIDS infants were more likely to have a gastrointestinal infection within two weeks prior to death. However we do not know how gastrointestinal infection relates to increased risk for SIDS.

Black infants are between two and three times as likely to succumb to SIDS. We do not know all the contributing factors that put black infants at greater risk. We do know that the incidence of low birth weight is higher among blacks than whites and some studies have demonstrated higher prevalence of smoking among black pregnant women than whites. Native Americans on the Aberdeen reservation have a five times greater incidence of SIDS than the national average. We would like to initiate a study in conjunction with the Indian Health Service to understand what is contributing to this high rate among this population.

Mr. Hoyer. Could you update us on the current status of the five year research plan for SIDS -- are we on schedule?

Dr. Alexander. We are currently operating in the first year of the five year plan. We have convened a group of experts to revise the current definition of SIDS so that we can be assured that cases used for research purposes meet minimal criteria for the SIDS diagnosis. These include that the infant be under one year of age, and that a complete postmortem investigation including, review of case history, autopsy, and death scene investigation is required.

We will soon be issuing a request for R&D contract proposals for a Brain Bank for Developmental Disorders. Tissues from SIDS victims, with accompanying medical and family histories, are a high priority acquisition for the bank. However this initiative will be reduced in scope from that outlined in the five year plan in that the medical examiner training and services needed for uniform nationwide collection of tissues will not be supported.

The pilot clinical trial for home monitoring will not be initiated as proposed in the first year of the plan, because

research proposals have not been of sufficient scientific merit. Further new scientific considerations obtained from expert consultants suggest that it would be more advantageous initially to solicit proposals for studies of life-threatening events detected at home by apnea monitors in high risk infants. This initiative is planned for release and funding in Fiscal Year 1991.

An Interagency Panel on SIDS has been established with representatives from relevant agencies in the Public Health Service. Panel discussions will generate interagency studies as outlined for the second year of the five-year plan.

A workshop is being held this fall on the development of animal models for SIDS and a workshop is being planned on the development of specific components of the immune system that may contribute to SIDS pathogenesis.

Therefore, with the exception of a one year delay in the study of apnea monitoring, we are on schedule.

SUBSTANCE ABUSE IN PREGNANCY

Mr. Hoyer. What is the impact of crack cocaine on the babies born to substance abusing parents in the near term and throughout their childhood; does the age of the substance abusing parent have an impact on the outcome for the infant?

Dr. Alexander. Unlike potent teratogens, such as thalidomide, whose gross malformations at birth issued warning flags, the morphological consequences of cocaine abuse during pregnancy are subtle. A major caveat in identifying the teratology of crack use is that it is part of a spectrum of problems which include the use of other substances of abuse, as well as alcohol and tobacco, poor or nonexistent prenatal care, and the risk of HIV infection. The effects of maternal cocaine abuse on the neonate can be attributed to its vasoconstrictive properties and to the fact that cocaine-dependent women exhibit multiple vitamin deficiencies. Affected babies are frequently premature or growth retarded at birth, and such birth defects as microcephaly and genitourinary malformations have been attributed to maternal cocaine abuse. A second problem that will need to receive greater emphasis will be to identify the neurological changes that result from maternal crack abuse. Studies on animal models have shown that cocaine is selectively concentrated in the fetal brain, suggesting that it may perturb normal neural development. Crack babies are reported to have an increased risk of microcephaly and cerebral infarctions. Recent studies on long term effects have shown that these children exhibit deficiencies in learning and socialization at 18 months of age. These preliminary data suggest that these children are placed at a disadvantage both in learning potential and in emotional development. As they mature, they will comprise a population of suboptimal performers.

Mr. Hoyer. What is the impact of substance abuse on pregnant teenagers?

Dr. Alexander. We are unaware of any studies that have shown that the age of the substance abusing parent has an impact on the outcome for the infant.

CHILDHOOD INJURY PREVENTION

Mr. Hoyer. Dr. Alexander, the Committee funds an injury control program at the CDC for about $22 million, and I am interested in what you can tell us about research on childhood injury.

Dr. Alexander. NICHD has implemented a multifaceted research initiative aimed at expanding our knowledge about the factors and mechanisms related to safety and risk behavior in children and identifying interventions which have a potential for reducing childhood injury, the major cause of death and disability in children after the first year of life.

Six projects seek to identify the characteristics of high risk populations so that those populations can be targeted for specific interventions. Among the variables being examined are child development, temperament and behavior, parent temperament, personality and locus of control, and family environment. Another group of projects explores new approaches for improving parent and/or child behavior related to child safety.

Several projects are exploring passive strategies which change the environment of the individual at risk. For example, one project aims to reduce unintentional poisonings in small children by developing improved child resistant medicine containers that rely on the differences in cognitive skills between young children and older adults. Other projects are targeting swimming pool drownings, electrical hazards, and the effects of frequent exposure to dangerous and high risk behavior on television.

SURVEY OF HEALTH AND AIDS RISK PREVALENCE

Mr. Hoyer. What is the proposed survey of health and AIDS risk prevalence and what will we learn from it?

Dr. Alexander. The Survey of Health and AIDS Risk Prevalence is a study of the behaviors that put adult Americans at risk of AIDS and other sexually transmitted diseases. To understand why some people choose behaviors that put them at risk and others do not, the study will include people scientifically chosen to represent the general population, not just people who belong to groups in which AIDS is relatively common.

The current project is a feasibility study involving approximately 2,300 individuals age 18-54. The results of this effort will show us whether people will be willing to respond to questions about their sexual behaviors, and it will provide answers to questions about how best to gather data on sexual behaviors.

Decisions about the size, scope and cost of the full scale survey will depend on the results of the feasibility study. However, as currently envisioned, the full-scale study would be designed to:

- provide accurate estimates of the number of people currently engaging in behaviors that put them at risk of HIV infection;

- o provide information to help predict and control the future pattern of spread of HIV infection and AIDS;

- o provide knowledge upon which to base HIV prevention and control programs;

- o increase understanding of the knowledge, attitudes and behavior that lead to transmission of other sexually transmitted diseases and unintended pregnancy.

Mr. Hoyer. What are the current and alternative sources of this type of information -- is this a good place to spend our money?

Dr. Alexander. Previous data are extremely out-of-date. They were collected before the social changes occurring in America during the last 30 years. The use of the outmoded data to describe today's behaviors is inappropriate. More recent magazine poll data cannot be used to represent the U.S. population, because they come only from readers of the particular magazine doing the survey and not the population as a whole. Other studies have collected information from small groups, such as clients at sexually transmitted disease clinics or drug abusers, or from a relatively small geographic region, neither of which can be generalized to the U.S. population as a whole.

This study has been called for by almost every scientific group assessing the AIDS epidemic. These data will help us model the likely spread of the AIDS epidemic. The behaviors that put people at risk of HIV infection also put people at risk for other sexually transmitted diseases and unwanted pregnancies. By gaining a better understanding of these behaviors, we not only help in the fight against AIDS but also gain information that can be used to enhance efforts in other areas of public health. AIDS is a compelling problem that must be addressed but we cannot and have not lost sight of the larger health concerns that face our population.

Mr. Hoyer. Is there reason to believe the study results would be biased?

Dr. Alexander. No. In addition to the well qualified team of investigators, many other people collaborated on the design of the study to ensure that the results are scientifically sound and unbiased. The study has a National Advisory Panel consisting of scientists representing many disciplines such as sociology, psychology, economics, demography, statistics, public health, and medicine. Comments from representatives of Public Health Service agencies including the National Institute of Child Health and Human Development, the Centers for Disease Control, the National Institute of Mental Health and the National Institute on Aging have been incorporated into the questionnaire. The National Advisory Child Health and Human Development Council has carefully reviewed and endorsed the study.

Once the data have been collected, a public use data set, with no individual identifying information, will be made available. This will allow researchers with a wide range of interests to analyze the data themselves.

Mr. Hoyer. How much will the study cost?

Dr. Alexander. The feasibility study of 2,300 people will cost about $2 million. It has been alleged that the study will cost $15 million, however, the costs for the full-scale study are unknown at this point and will depend on the results of the feasibility study.

Mr. Hoyer. How will people be picked to participate in the study and is it entirely voluntary?

Dr. Alexander. People will be chosen scientifically by demographic characteristics so that the sample is representative of the U.S. population. To understand why some people choose behaviors that put them at risk of contracting sexually transmitted diseases and others do not, it is essential that participants be drawn from across the U.S. and not selected on the basis of any characteristics associated with an increased risk of HIV infection. The study will include people who range from being at no risk of infection to high risk of infection.

Before the interview is begun, people are informed about the content of the questionnaire and told that participation is entirely voluntary. If they begin the interview but do not want to continue they may terminate at any point. Respondents also have the option of refusing to answer any individual question. During the development of the survey, the questions that are included were asked of many American citizens and found to be acceptable. However, one of the major purposes of the feasibility study is to determine what level of participation we could expect in a large national study.

Mr. Hoyer. How will the privacy of participants be protected?

Dr. Alexander. Data collected in the feasibility study are protected by Section 308 (d) of the Public Health Service Act (42 U.S.C 242m). This means that data on individuals cannot be obtained by anyone. A certificate of confidentiality also will be obtained for the study which provides further protection against release of information about people participating in health research. The contractor's procedures for gathering and storing data ensure that names and data are not linked.

Mr. Hoyer. Are funds included in the budget to undertake the survey?

Dr. Alexander. Funds for the feasibility study were provided in FY 1988. The feasibility study has been delayed and may require additional funds in FY 1991 to complete it. There are no funds in FY 1990 or FY 1991 for a full-scale study, because such a study will not be contemplated until we have considered the feasibility study experience. The feasibility study is still under review at PHS by Dr. Mason at the present time.

LEVEL OF FUNDING

Mr. Pursell. The Administration has proposed to spend $461 million on your Institute in FY 91. Do you believe this is a sufficient level of funding to support your needs?

Dr. Alexander. Although we could always put additional funds to good use, we recognize that the President's Budget is always developed within the constraints of many competing demands and limited resources. The FY 1991 budget request for the NICHD will allow us to continue our major initiatives with our basic funding philosophy -- to fund only the very best research.

Mr. Pursell. Approximately one-fourth of our nation's population are children, yet the National Institute of Child Health and Human Development receives less than six percent of the NIH budget. Is this appropriate?

Dr. Alexander. The NICHD has accounted for approximately 6 percent of the total NIH budget for over 20 years, even though it does not coincide with the proportion of children in the population. Research on specific childhood diseases is conducted in many other NIH institutes, so the total proportion of the NIH budget attributable to children would be considerably more than just the NICHD share.

Mr. Pursell. What level of approved research projects do you fund and how does this compare with other Institutes?

Dr. Alexander. In FY 1991, the NICHD will fund approximately 22.5 percent of approved applications. The average award rate for NIH in FY 1991 is 25.5 percent.

REHABILITATION RESEARCH

Mr. Pursell. Many rehabilitation researchers and advocates are supporters of a more coordinated child health rehab effort at your Institute, and argue that a National Center for Child Rehabilitation Research should be established at NICHD. Do you support this proposal?

Dr. Alexander. The NIH uses a variety of mechanisms to assure coordination of research programs that overlap the interests of more than one of our research Institutes. For this important area of medical rehabilitation, including the special needs of children, we have established an inter-Institute committee to review and make recommendations on needs for research as well as the optimal administrative structure to manage these programs. The committee's work is under way.

Mr. Pursell. How do the rehabilitation needs of children differ from those of seniors, who are the primary subjects of rehab research conducted by the National Institute of Aging and National Institute on Neurological Diseases and Stroke?

Dr. Alexander. The rehabilitation needs of infants, children, adolescents, and young adults share some of the same medical and psychosocial research approaches with neurologic and geriatric

populations. Medical management of disabilities in all these categories include treatment of disorders of eating, toileting, mobility, and pain, and behavioral, cognitive, and emotional adjustment to functional loss(es) by the disabled individual, his/her family, his/her support network, and the larger community. The unique aspect of rehabilitation of physically impaired infants, children, adolescents, and young adults is that they are in stages of development where the consequences of a physical impairment can have devastating effects in their development for the remainder of life. At the same time, the plasticity or ability to change is great in younger populations. Thus, the early, effective intervention by the rehabilitation team to reduce the impact of a functional loss to a developing child will involve some groups not usually involved in the management of geriatric populations. For example, the child's parents, siblings, playmates, educators, vocational counselors, and employers would be important team members in efforts to reduce the chances of the child developing unnecessary life long dependencies. This could best be accomplished by managing the child's long term care in an atmosphere which encourages the development of a variety of compensatory skills that fit within the normally accepted boundaries of development. With these skills, the physically impaired young adult can, in many cases, minimize the effects of a physical impairment and become engaged in a fulfilling life as a part of their larger community. The NICHD has sponsored research on the course of physical and behavioral development of normal and developmentally disabled individuals from infancy through adulthood. The integration of individuals with developmental disabilities into the mainstream of American culture has been accelerated through these efforts. The theories, methods, and findings of these research projects have produced a framework that could serve as a firm basis for longitudinal, multidisciplinary studies of individuals with physical impairments. The goal of such studies would be to improve our knowledge base, to develop new techniques and treatment and to implement better medical and psychosocial rehabilitation for individuals with physical impairments.

CHILD HEALTH RESEARCH CENTERS

Mr. Pursell. Please provide an update for the record on the Child Health Research Centers program, which would provide resources to transfer NICHD research results to clinical applications.

Dr. Alexander. The NICHD has initiated procedures to award funds for these Centers. A set of guidelines was developed and over 150 copies of a request for application were distributed. Institute staff have been assisting pediatric departments throughout the U.S. in the preparation of applications. Between 30 and 50 strong applications are expected by the specified receipt date of April 23, 1990, with review scheduled for July-September. It is anticipated that from five to seven awards to establish Child Health Research Centers will be made before the end of the fiscal year.

REPRODUCTIVE SCIENCES RESEARCH

Mr. Pursell. Regarding human development, the University of Michigan's Reproductive Sciences Program is one of the best in the world. Are we close to any significant breakthroughs in this area?

Dr. Alexander. Over the past few years, we have experienced particularly significant gains in our understanding of the genetic mechanisms guiding the determination of the male or female sex in the human. Using the high powered tools of recombinant DNA technology, DNA sequences have been identified which are involved in the embryo's decision to develop either the male or female gonads and reproductive tract. Cloning and analyzing the Y chromosome DNA sequences associated with testis formation and resident germ cell functioning has already greatly expanded our understanding of the genetic basis of disorders in sex determination and fertility arising from misadventures of these gene sequences. We are happy to acknowledge that researchers at the University of Michigan have played an important role in the progress being achieved in this field.

CHILD HEALTH RESEARCH CENTERS

Mr. Porter. Dr. Alexander, last year we discussed Child Health Research Centers. I am pleased to see that you included a request for "five or six" of these centers. Under your budget request, at what level will these centers be funded?

Dr. Alexander. In FY 1991, the NICHD proposes to fund six child health research centers at approximately $1,882,000.

Mr. Porter. How many centers do you propose for FY 92?

Dr. Alexander. While the NICHD has not yet prepared a FY 1992 preliminary budget, I would expect that we would at least continue support of the six centers whose grants carry over from FY 1991.

Mr Porter. How much would you need to adequately support 10 centers?

Dr. Alexander. Support of 10 child health research centers in FY 1991 would require approximately $3,136,000.

SURVEY OF HEALTH AND AIDS RISK PREVALENCE

Mr. Porter. Last year I also asked about your survey of sexual behavior. What is the status of this effort?

Dr. Alexander. The Survey of Health and AIDS Risk Prevalence (SHARP) is a feasibility study which will provide interim measures of risk behaviors and help to determine how, and if, to proceed with a large scale national effort. This survey is part of our program of research designed to help us to understand better the behaviors that put people at risk of sexual transmission of AIDS and to assess the likely level and pattern of spread of the epidemic. While we all seek a cure for AIDS, it is important to understand the behaviors that lead to risk of infection. Secretary Sullivan has asked for a thorough review of this feasibility study to ensure that it balances scientific need with public acceptability. NIH has completed its review of the project and forwarded it to Dr. Mason, the Assistant Secretary for Health.

CONTRACEPTIVE RESEARCH

Mr. Porter. What is the status of your contraceptive research effort? Are any private sector firms conducting contraceptive research?

Dr. Alexander. The Institute is currently supporting clinical trials involving new drugs and devices, including drug delivery systems, disposable diaphragms, and new spermicidal agents which may be attractive to a wide segment of the U.S. population. At the preclinical or laboratory level, we are also pursuing synthesis and testing of new drugs, development of new barrier methods, development of new methods of drug delivery, newer and safer condoms, and the exploration of antifertility vaccines.

In the United States, there is only one pharmaceutical company which is still conducting contraceptive research.

Mr. Porter. What role does liability play in your contraceptive research effort? Is the liability situation getting better or worse?

Dr. Alexander. Product liability considerations have had a substantial impact on the NIH contraceptive development program. In many instances, NIH contractors have lost their product liability insurance and could not purchase new insurance policies because of the tremendous premium escalation. In addition many insurance companies now refuse to provide insurance for clinical investigations. Thus the liability situation has not improved.

Mr. Porter. What recommendations would you make to improve the liability climate?

Dr. Alexander. Considering experience from the NICHD research programs, it appears that the liability situation might be improved by protection for government agencies, private institutions, and pharmaceutical companies in the development and testing of new contraceptives. Innovations might cover third party liability insurance, limits on damages to volunteers in clinical trials, and indemnification of researchers for careful adherence to FDA testing guidelines.

RESEARCH CENTERS

Mr. Porter. Assuming that this subcommittee provides you with increased funding for centers, would you expand the number of funded centers, or would you increase funding for those centers that are already in operation?

Dr. Alexander. We would first use any additional funds to increase the funding for centers already in operation, hence decreasing the projected rate of downward negotiation. Subsequent additional funds would be used to expand the number of centers, although within already existing center programs, such as the mental retardation research centers, the population research centers, and the child health research centers.

SUDDEN INFANT DEATH SYNDROME

Mr. Weber. Dr. Alexander, what is the current status of the 5-year Sudden Infant Death Syndrome Research Plan?

Dr. Alexander. We are currently operating in the first year of the five-year plan. We have convened a group of experts to revise the current definition of SIDS so that we can be assured that cases used for research purposes meet minimal criteria for the SIDS diagnosis -- the infant is under one year of age, and a complete postmortem investigation including review of case history, autopsy, and death scene investigation is conducted.

We will soon be issuing a request for R&D contract proposals for a Brain Bank for Developmental Disorders. Tissues from SIDS victims, with accompanying medical and family histories, are a high priority acquisition for the bank.

The pilot clinical trial for home monitoring will not be initiated as proposed in the first year of the plan, because research proposals have not been of sufficient scientific merit. Further, new scientific considerations obtained from expert consultants suggest that it would be more advantageous initially to solicit proposals for studies of life-threatening events detected at home, by apnea monitors, in high risk infants. This initiative is planned for funding in FY 1991.

An Interagency Panel on SIDS has been established with representatives from relevant agencies in the Public Health Service. Panel discussions will generate interagency studies as outlined for the second year of the five year plan.

Mr. Weber. What are the things that should be done to continue to implement the 5-year SIDS Research Plan?

Dr. Alexander. In the second year of the five year plan, the scope of the Brain Bank should be expanded to include more SIDS tissues and registry information and a program for medical examiner training and services that are needed for uniform nationwide collection of tissue.

An interagency study of the high incidence of SIDS among specific Native Americans populations is needed to learn more about the risk factors for SIDS and the impact and cause of sudden unexpected deaths in the Native American population.

A workshop is being held this fall to define the research necessary to generate and study useful animal models of SIDS. A specific research initiative in this area is needed so that we are able to explore developmental etiologies of SIDS and test the effects of environmental stresses and interventions.

A specific research initiative is necessary on the role of the immune system in the pathogenesis of SIDS. A workshop is being planned to explore what we need to learn about the maturation and vulnerability of the pulmonary and gastrointestinal immune systems and the interaction of the immune system with those parts of the nervous system that control cardiorespiratory function.

The Institute is also considering a companion clinical study to the planned apnea monitoring study which will examine relevant physiologic and behavioral parameters in early infancy which may serve as prognostic clinical tests to identify infants at risk for SIDS.

Mr. Weber. What additional funding is necessary to implement the 2nd year of the 5-year plan?

Dr. Alexander. The NICHD would require an additional $6 million to implement fully the second year of the SIDS 5-year Plan.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

FY 1991 Budget

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NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

For carrying out section 301 and Title IV of the Public Health Service Act with respect to child health and human development, [$450,593,000] *$461,473,000*.

(Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 1990.)

NATIONAL INSTITUTES OF HEALTH 3

National Institute of Child Health and Human Development

Amounts Available for Obligation 1/

	1989 Actual	1990 Appropriation	1991 Estimate
Appropriation	$431,388,000	$450,593,000	$461,473,000
Enacted administrative reduction	-5,739,000	-1,506,000	---
Sequester order	---	-6,173,000	---
Subtotal, adjusted appropriation	425,649,000	442,914,000	461,473,000
Real transfer to the Office of the Assistant Secretary for Health for AZT grants	-274,000	---	---
Comparative transfers to:			
Fogarty International Center, NIH, for passport activities	-8,000	-8,000	---
Division of Research Resources, NIH for administrative cost of the RCMI program	-13,000	---	---
Comparative transfer from:			
Office of the Director, NIH for FTE increase	+564,000	---	---
Subtotal, adjusted budget authority	425,918,000	442,906,000	461,473,000
Unobligated balance lapsing	-107,000	---	---
Total obligations	425,811,000	442,906,000	461,473,000

1/ Excludes the following amounts for reimbursable activities carried out under this account: 1989 -- $2,953,000; 1990 — $3,000,000; 1991 — $3,000,000.

Excludes $9,000 for royalties received in 1989.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Budget Mechanism
(Dollars in thousands)

	1989 Actual		1990 1/ Appropriation		1991 Estimate	
Research grants:	No.	Amount	No.	Amount	No.	Amount
Research projects						
Noncompeting	1,051	$184,474	1,109	$202,960	1,069	$203,593
Admin. supplementals	(87)	4,219	(40)	1,262	(50)	1,712
Competing:						
Renewal	159	30,826	127	27,483	144	33,302
New	269	40,392	191	31,813	213	38,547
Supplemental	5	339	5	516	5	529
Subtotal, competing	433	71,557	323	59,812	362	72,378
Subtotal, res. proj	1,484	260,250	1,432	264,034	1,431	277,683
Research centers						
Specialized/comp. centers	46	33,408	53	36,914	53	36,914
Other research						
Research career program	98	6,619	113	7,930	113	7,930
Coop. clin. research	6	903	6	1,282	6	1,282
Minor. biomed. res. support		509		524		569
Other research related	68	2,983	63	2,958	63	2,958
Subtotal, other research	172	11,014	182	12,694	182	12,739
Total, research grants	1,702	304,672	1,667	313,642	1,666	327,336

Training						
Individual awards:						
Noncompeting.....	55	1,513	49	1,379	78	2,187
Competing						
Renewal.....	0	0	0	0	0	0
New.....	31	794	59	1,614	30	806
Subtotal, individ.....	86	2,307	108	2,993	108	2,993
Institutional awards:						
Noncompeting.....	435	9,133	478	11,184	506	11,818
Competing						
Renewal.....	105	2,093	81	1,861	65	1,498
New.....	14	362	23	518	11	253
Subtotal, inst.....	554	11,588	582	13,563	582	13,569
Total, training.....	640	13,895	690	16,556	690	16,562
Research and development contracts.....	110	35,735	124	35,221	124	35,808
	FTEs		FTEs		FTEs	
Intramural research.....	263	50,396	261	54,757	264	58,959
Research management and support.....	175	21,220	173	21,776	176	22,808
Extramural construction.....		---		954		---
Total.....	438	425,918	434	442,906	440	461,473
HIV/AIDS.....	(21)	(22,704)	(22)	(26,749)	(25)	(29,010)

1/ Includes approximately $954,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

CROSSWALK - 1989 Actual

(Dollars in thousands)

PROGRAM ACTIVITY	MECHANISM								
	Research Grants			Training Programs		Research and Development Contracts	Intramural Research	Research Management and Support	Total
	Research Projects	Research Centers	Other Research	Individual	Institutional				
Research for mothers & children...	$171,047	$17,853	$7,992	$1,305	$8,116	$22,208	---	---	$228,521
Population research....	89,203	15,555	3,022	1,002	3,472	13,527	---	---	125,781
Intramural research....	---	---	---	---	---	---	$50,396	---	50,396
Research management and support.....	---	---	---	---	---	---	---	$21,220	21,220
Total.....	260,250	33,408	11,014	2,307	11,588	35,735	50,396	21,220	425,918

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

CROSSWALK - 1990 Appropriation[1/]

(Dollars in thousands)

PROGRAM ACTIVITY	MECHANISM									
	Research Grants			Training Programs		Research and Development Contracts	Intramural Research	Research Management and Support	Extramural Construction	Total
	Research Projects	Research Centers	Other Research	Individual	Institutional					
Research for mothers and children.....	$175,714	$21,103	$9,511	$1,693	$9,511	$20,210	---	---	---	$237,742
Population.....	88,320	15,811	3,183	1,300	4,052	15,011	---	---	---	127,677
Intramural research....	---	---	---	---	---	---	$54,757	---	---	54,757
Research management and support.....	---	---	---	---	---	---	---	$21,776	---	21,776
Extramural Construction	---	---	---	---	---	---	---	---	$954	954
Total.....	264,034	36,914	12,694	2,993	13,563	35,221	54,757	21,776	954	442,906

1/ Includes approximately $954,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

CROSSWALK - 1991 Estimate

(Dollars in thousands)

PROGRAM ACTIVITY	MECHANISM								
	Research Grants			Training Programs		Research and Development Contracts	Intramural Research	Research Management and Support	Total
	Research Projects	Research Centers	Other Research	Individual	Institutional				
Research for mothers & children...	$184,703	$21,103	$9,545	$1,693	$9,517	$20,680	---	---	$247,241
Population.....	92,980	15,811	3,194	1,300	4,052	15,128	---	---	132,465
Intramural research....	---	---	---	---	---	---	$58,959	---	58,959
Research management and support.....	---	---	---	---	---	---	---	$22,808	22,808
Total.....	277,683	36,914	12,739	2,993	13,569	35,808	58,959	22,808	461,473

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Summary of Changes

1990 Estimated budget authority	$442,906,000
1991 Estimated budget authority	461,473,000
Net Change	+18,567,000

Changes:	1990 Current Estimate Base Pos. (FTEs)	1990 Current Estimate Base Budget Authority	Change from Base Pos. (FTEs)	Change from Base Budget Authority
A. Built-in:				
1. Within grade increase		$26,574,000		+$469,000
2. Annualization of January 1990 pay raise		26,574,000		+236,000
3. One extra day of pay		26,574,000		+101,000
4. January 1991 pay raise		26,574,000		+958,000
5. Federal Employees Compensation Fund		85,000		+3,000
6. Unemployment compensation increase		40,000		+1,000
7. FTS rate increase		416,000		+13,000
8. Payment for centrally furnished services		23,392,000		+838,000
9. Service and supply fund increase		11,679,000		+409,000
10. Increased costs for services and supplies		26,567,000		+526,000
11. Other built-in laboratory and other animal holding cost increases		20,311,000		+1,000,000
12. DHHS Working Capital Fund		487,000		-23,000
Subtotal				+4,531,000
B. Program:	No.	Amount	No.	Amount
1. Research project grants:				
a. Noncompeting	1,109	204,222,000	-40	+1,083,000
b. Competing	323	59,812,000	+39	+12,566,000
Total	1,432	264,034,000	-1	+13,649,000
2. Other research		12,694,000		+45,000
3. Research training		16,556,000		+6,000
4. Research and development contracts	FTEs	35,221,000	FTEs	+587,000
5. Intramural research	261	54,757,000	+3	+490,000
6. Research Management and Support	173	21,776,000	+3	+213,000
7. Extramural construction		954,000	—	-954,000
Subtotal				+14,036,000
Total changes				+18,567,000

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NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Budget Authority by Activity
(Dollars in thousands)

	1989 Actual		1990 1/ Appropriation		1991 Estimate	
	FTEs	Amount	FTEs	Amount	FTEs	Amount
Research for Mothers and Children.....		$228,521		$237,742		$247,241
Population Research.....		125,781		127,677		132,465
Intramural Research.....	263	50,396	261	54,757	264	58,959
Research Management and Support.....	175	21,113	173	21,776	176	22,808
Extramural Construction.	---	---	---	954	---	---
Total, Obligations.....	438	425,811	434	442,906	440	461,473
Unobligated Balance, Lapsing.....	---	107	---	---	---	---
Total, Budget Authority.	438	425,918	434	442,906	440	461,473
HIV/AIDS.....	(21)	(22,704)	(22)	(26,749)	(25)	(29,010)

1/ Includes approximately $954,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Budget Authority by Object

	1990 Appropriation	1991 Estimate	Increase or Decrease
Total number of full-time permanent positions	335	335	---
Total compensable work years:			
Full-time equivalent employment	447	453	+6
Full-time equivalent of overtime and holiday hours	7	7	---
Average ES salary	$79,200	$100,395	+$21,195
Average GM/GS grade	9.9	9.9	---
Average GM/GS salary	$36,727	$38,012	+$1,285
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	$68,658	$71,061	+$2,403
Average salary of ungraded positions	$23,944	$23,944	---
Personnel compensation:			
Full-time permanent	$14,309,000	$15,571,000	+$1,262,000
Other than full-time permanent	4,700,000	5,100,000	+400,000
Other personnel compensation	1,100,000	1,150,000	+50,000
Special personnel service payments	2,400,000	2,500,000	+100,000
Total personnel compensation	22,509,000	24,321,000	+1,812,000
Personnel benefits	4,065,000	4,393,000	+328,000
Benefits for former personnel	20,000	20,000	---
Travel and transportation of persons	1,200,000	1,300,000	+100,000
Transportation of things	160,000	160,000	---
Rent, communications, and utilities	1,900,000	2,000,000	+100,000

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	1990 Appropriation	1991 Estimate	Increase or Decrease
Printing and reproduction.....	400,000	400,000	---
Other services:			
Project contracts.....	35,221,000	35,808,000	+587,000
Centrally furnished services.....	22,379,000	23,496,000	+1,117,000
Standard level user's charge.....	1,013,000	734,000	-279,000
Other.....	13,487,000	14,543,000	+1,056,000
Supplies and materials.....	6,300,000	6,800,000	+500,000
Equipment.....	3,100,000	3,600,000	+500,000
Grants, subsidies, & contributions....	331,152,000	343,898,000	+12,746,000
Total Budget Authority.....	442,906,000	461,473,000	+18,567,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Significant Items in House and Senate Appropriations Committee Reports

Item	Action Taken or to be Taken
1990 House Report	
Contraceptive Development	
1. The Committee remains concerned about the high rate of unintended pregnancy among U.S. women and the lack of new and improved methods of contraception that are safe, effective, inexpensive, reversible and acceptable to various segments of the population. The role of the NICHD in responding to this serious situation remains critical in light of the small number of private sector companies active in this field. The Committee urges the Institute to place a greater priority on funding its ongoing initiative on contraceptive research and development. (Page 71).	1. The Institute shares the Committee's concern about the high rate of unintended pregnancy among U.S. women. Within the resources allocated to NICHD, every effort is being made to move forward with the development of improved methods of contraception. The Institute supports research that will result in the availability of new drugs and devices to be used for fertility regulation. The process of developing new contraceptive products, however, is complex and requires extensive testing for both efficacy and safety. Recognizing that the resources for contraceptive product development are limited, the Institute has established collaboration with other public sector agencies in order to avoid duplication of effort and to maximize progress.
Monitoring High Risk Women	
2. The Committee has been advised of the success of monitoring women at high risk for pre-term birth. The Institute is encouraged to incorporate research in this area into the existing centers programs to determine the value of monitoring as a means of lowering infant mortality and morbidity. (Page 71).	2. NICHD sponsored a workshop in the Spring of 1989, to assess the status of home uterine monitoring to detect and predict preterm labor. NICHD is currently supporting, in collaboration with the Bureau of Maternal and Child Health and Resource Development (BMCHRD), HRSA, a research effort to define more clearly the normal contractile patterns of the uterus in the second half of pregnancy, so that deviations can be more readily recognized. In the recompetition of the existing Maternal-Fetal Medicine Units Network of

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Item	Action Taken or to be Taken
	clinical centers supported by NICHD, the RFA specifies a NICHD priority interest in clinical trials which evaluate uterine monitors and other techniques designed to reduce the risk of preterm labor and birth.
Rett Syndrome	
3. The Committee continues its strong interest in research related to Rett Syndrome, a genetic disorder affecting more than 10,000 patients. The Committee has specifically added money so that this program can be expanded.(Page 72).	3. Two large program projects have been awarded by NICHD to investigate various aspects of the syndrome, including neurochemistry, neuropathology, neurophysiology, neuroimaging, and genetics. Investigators from the two institutions are collaborating with one another and are sharing scarce specimens. The absence of a diagnostic marker is a major stumbling block to our understanding of the fundamental basis of the syndrome. Continuation and expansion of ongoing research is vital in order to increase our understanding of the neuropathology of Rett syndrome. The Institute expects to increase FY 1990 funding in Rett Syndrome by $250,000 over the FY 1989 level.
Pediatric AIDS	
4. The Committee applauds the the NICHD commitment to providing $2 million in resources to Pediatric AIDS research laboratory and instrumentation needs, but believes this commitment is far from adequate. The Committee also encourages the NICHD to increase funding supporting research in early diagnosis methods, and in assisting established centers dedicated to Pediatric AIDS work to expand their capacity to undertake treatment and research at multiple sites. Therefore, the Committee recommends funds be set aside from the NICHD	4. The NICHD shares the interest of the Committee in devoting funding and technical support to Pediatric AIDS centers, especially in areas of high seroprevalence in child-bearing women. It concurs that emphasis must be placed on both targeted biomedical research and treatment research. The NICHD awarded over $3 million, early in FY'90, to six major pediatric AIDS centers to fund basic research in the development and evaluation of improved methods of the early diagnosis of HIV infection in infants and children. This is an addition to two other centers which are already funded. The NICHD continues to support 25 medical centers around the country (including three in Puerto Rico) to conduct therapeutic research in pediatric and eventually obstetric HIV infection and disease. Many are located in areas of high seroprevalence. This group of clinical research centers will be amalgamated with

Item	Action Taken or to be Taken
budget to assist in improved laboratory instrumentation and equipment needs of pediatric AIDS centers, as well as to support expanded site capacity and early diagnosis research. The Committee suggests that funds be set aside for centers located in urban areas of high sero-positive AIDS prevalency rates in newborns, which are dedicated to primarily serving minority and disadvantaged populations, and where there is already evidence of NIH-supported research and training, as well as support and collaboration with and from state and local agencies. (Page 72).	the NIAID-supported group of pediatric clinical trials centers in order that the majority of HIV-infected children in the U.S. will have the opportunity to participate in state-of-the-art research and care that is directed against AIDS. The majority of subjects enrolled in the NICHD centers are minority children from severely disadvantaged backgrounds. The funding to support this effort provides a large component of laboratory instrumentation support. Where appropriate, the NICHD interacts with local and state agencies to collaborate in the care and treatment of these children.
Child Health Research Centers	
5. The Committee encourages the Institute (NICHD) to explore the establishment of a child health centers program with grants to be awarded to academic/ clinical medical institutions whose primary mission is the care of children. The program would build the research capacity of such centers.(Page 73).	5. The NICHD has prepared an announcement soliciting applications for a new program of Child Health Research Centers. In these Centers competitively-funded, established investigators would assist pediatricians in developing new research projects applying the methods of basic science to pediatric problems. The Centers would include core laboratories which would expand their research capacities, providing a focus for the new research. It is anticipated that five to six such centers will be established in the first year.
Research Centers on Learning Disabilities	
6. The Committee is pleased with the progress made under the leadership of NICHD toward implementing the recommendations of the Interagency Committee on	6. In response to the direction provided by the Committee, the NICHD recently funded two multi-disciplinary research centers for the study of learning disabilities. A third center will be funded this year. The attention and

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Item	Action Taken or to be Taken
Learning Disabilities... Funding has been included in the bill for the establishment of a third new interdisciplinary research center on learning disabilities. (Page 73).	interest of the research community has been captured through the award of these research centers. Several distinguished scientists have joined the centers and we anticipate that the combined efforts of biological and behavioral scientists will bring progress toward the better understanding and treatment of individuals with learning disabilities.
1990 Senate Report	
Fertility Research	
1. The Committee continues to be interested in the ongoing efforts relating to fertility research in the Institute's centers program. Further, the Committee directs that continued emphasis in this important area of research will be a priority of the Institute in the coming year.(Page 137).	1. The center program supporting fertility research is a high-priority activity at the NICHD. The NICHD shares the Committee's interest in this important area of research and will continue to emphasize it. The NICHD has issued a request for applications (RFA) to enhance this program in the coming year. In addition, a new Multicenter Cooperative Agreement for Reproductive Medicine research involving clinical trials is being established this year. The latter activity will further emphasize our commitment to our major centers program in fertility research.
Infant Mortality Prevention	
2. The Committee urges NICHD to give priority under its existing centers program to exploring the feasibility of monitoring women at high risk in order to lower our Nation's infant mortality statistics. The Committee further feels that this would be an excellent example of a program that should be supported across Institutes, such as by the NICHD and the National Center for Nursing Research. (Page 138).	2. NICHD agrees that monitoring of woman at high-risk for preterm delivery is a promising strategy to reduce infant mortality. In accordance, the NICHD sponsored a workshop in the Spring of 1989 to assess the status of home uterine monitoring to detect and predict preterm labor. NICHD is currently supporting, in collaboration with BMCHRD, HRSA, a research effort to define more clearly the normal contractile patterns of the uterus in the second half of pregnancy, so that deviations can be more readily recognized. In the recompetition of the existing Maternal-Fetal Medicine Units Networks of clinical centers supported by NICHD, the RFA specifies a NICHD priority interest in clinical trials which evaluate uterine monitors and other techniques designed to

Item	Action Taken or to be Taken
	reduce the risk of preterm labor and birth. NICHD will encourage cooperation with NCNR on these studies to the extent feasible.
Collaborative Efforts with Professional Nurses	
3. The Committee is pleased with the efforts of the NICHD to ensure that professional nurses are actively involved in the programs of NICHD, particularly its collaborative efforts with the National Center of Nursing Research. NICHD is strongly urged to continue its efforts to ensure that professional nurses are actively involved in its activities and programs.(Page 139).	3. The NICHD shares the Committee's concern in the NICHD program, particularly in collaborative efforts with the National Center for Nursing Research(NCNR). The NICHD has recently issued a joint program announcement with NCNR for research on neonatal nursing care of low birth weight infants. In addition, the Pregnancy and Perinatology Branch staff, Center for Research on Mothers and Children, have been active participants on the first Priority Expert Panel of the National Nursing Research Agenda. NICHD plans to undertake future joint initiatives in perinatal/neonatal care research with NCNR.
Bush Centers	
4. The Committee understands that Bush Centers, previously funded privately, are losing their funding source. The Committee encourages the NICHD to explore the possibility of funding these centers within available resources and by using increased funding provided by the Committee.(Page 139).	4. It is our understanding that funds to partially support the existing four Bush Centers in Social Development and Child Policy, previously funded by the Bush Foundation of Minneapolis, Minnesota, were appropriated elsewhere in the Department.
Mental Retardation Centers	
5. The Committee has provided funding to continue funding 12 mental retardation centers...The Committee is aware, however, that two existing centers-one in Illinois and one in California-recently failed in	5. The Mental Retardation Research Centers (MRRCs) provide support for research and research training relevant to mental retardation and related aspects of human development. Research efforts in these centers have provided much of the empirical bases for the advances in fundamental knowledge of the many causes of mental retardation, in the early

Item	Action Taken or to be Taken
competition to be renewed. These two centers competed very strongly and it is the Committee's view that they should be continued, if possible, with available funds. The Committee believes that adequate funding is available, both within the base and from increases provided, to continue these two centers.(Page 139).	diagnosis and prevention of a wide variety of developmental disabilities, and in improving the function and adaptation of those who are developmentally disabled. Since 1987, the NICHD opened the competition for these centers to any institution possessing the requisite programs for conducting excellent research and training in the field of developmental disabilities. The two existing centers that failed in competition to be renewed were provided with sufficient NICHD funds to regroup and prepare an amended application for competitive review. It will not be possible, however, at the current budget level, to provide funding for more than twelve mental retardation centers.
Infant Day Care	
6. Infant day care is one of the most important policy issues for the future of our children and families...Therefore, the Committee urges the NICHD to pursue the full range of projects within the consortium of studies on infant day care.(Page 140).	6. The NICHD shares the Committee's view that infant day care is an important policy issue for both the American family and the public and private institutions that employ our Nation's workforce. Accordingly, NICHD is funding a cooperative network to prospectively study the effects of different types of infant day care upon the social and emotional development of children during the first three years of life. Initially the network was composed of six participating sites. Recently, the Institute expanded that number to ten sites. This addition will enhance the capacity to gather an in-depth knowledge of childrens' development over a more representative geographical distribution of the country. Expanding to the 10 sites insures that the full range of projects will be pursued.
1990 Conference Report	
SIDS Research and Infant Monitoring	
1. The Committee continues to recognize the importance of a controlled	1. The NICHD shares the Committee's concern regarding the need for preventive intervention for SIDS. Two proposals to

Item	Action Taken or to be Taken
study of the use of infant apnea monitoring and is concerned that the NICHD has been slow to achieve this objective. To that end the conference agreement includes funding for the implementation of the first year of the 5 year plan for sudden infant death syndrome research, applauds the other important and meritorious SIDS research initiatives outlined in the plan, and recommends implementation in an expeditious manner.(Page 21).	test apnea monitors were unsuccessful after peer review in 1989. The NICHD will convene a group of experts in January 1990, to discuss the design and conduct of studies of monitoring and cardio-respiratory control. An initiative for a large-scale prospective study will be published in FY 1990 and funded in FY 1991. Among the SIDS initiatives outlined in the first five year SIDS research plan was a review of the diagnosis of SIDS. A workshop of experts convened in June 1989 redefined SIDS for all NICHD research. NICHD and HRSA Interagency Panel on SIDS will reconvene in February 1990 to design and coordinate SIDS research. Conferences scheduled for FY 1990 include animal models of SIDS and immunological response of infants to infection.

29-452 O—90——36

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1990 Amt. Authorized	1990 Estimate	1991 Amt. Authorized	1991 Budget Estimate
Research and Investigation..	Section 301	42§241	Indefinite	$426,350,000	Indefinite	$444,911,000
National Institute of Child Health and Human Development.....	Title IV, Subpart 7	42§285g	Indefinite		Indefinite	
National Research Service Awards.....	Section 487	42§288	Such Sums as Necessary 1/	16,556,000	Authorizing Legislation to be Requested 1/	16,562,000
Total, Budget Authority...				442,906,000		461,473,000

1/ This training authority is shared with other research training programs of the National Institutes of Health and the Alcohol, Drug Abuse, and Mental Health Administration.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Appropriations History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1982	203,362,000 2/	238,411,000	236,248,000	226,309,000
1983	233,575,000	251,561,000	257,087,000	254,324,000
1984	256,592,000	266,047,000 3/	265,714,000 3/	276,046,000
1985	280,178,000	296,929,000 4/	316,100,000	313,295,000
1986	293,084,000	306,812,000 5/	323,071,000	321,796,000
1986 Sequester				-13,838,000
1987 6/	309,119,000	368,509,000	362,866,000	366,780,000
1988	322,032,000	405,673,000 7/	408,334,000	396,811,000
1989	397,945,000 8/	407,650,000 9/	431,388,000	425,649,000 10/
1990	417,064,000 11/	448,493,000	450,593,000	449,087,000 12/
1990 Sequester				-6,173,000
1991	461,473,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.
2/ Reflects the September amendment; the original request was $231,093,000.
3/ Excludes $9,297,000 in NRSA training programs not considered.
4/ Excludes $9,831,000 in NRSA training programs not considered.
5/ Excludes $13,901,000 in NRSA training programs not considered.
6/ The Budget Estimate to Congress proposed that all funding for AIDS research be consolidated in the Office of the Assistant Secretary for Health. The House Allowance consolidated all NIH AIDS funding in the Office of the Director, NIH; the Senate Allowance spread the funding among the Institutes, including $2,186,000 for NICHD.
7/ Does not include funding for AIDS research. Consolidated at the Secretary's level.
8/ The 1989 request excludes funds for AIDS research and education ($20,443,000) proposed for consolidation in the Office of the Assistant Secretary for Health.
9/ Excludes $14,738,000 in NRSA training programs not considered.
10/ Excludes enacted administrative reduction of $5,739,000.
11/ The 1990 request excludes funds for the National HIV program ($27,129,000) proposed for consolidation in the Office of the Assistant Secretary for Health.
12/ Excludes enacted administrative reduction of $1,506,000.

Justification

National Institute of Child Health and Human Development

	1990 Appropriation		1991 Estimate		Increase or Decrease	
	FTEs	BA	FTEs	BA	FTEs	BA
TOTAL....	434	$442,906,000	440	$461,473,000	+6	+$18,567,000
HIV/AIDS.	(22)	(26,749,000)	(25)	(29,010,000)	(+3)	(+2,261,000)

General Statement

The National Institute of Child Health and Human Development (NICHD) is the focal point at the National Institutes of Health (NIH) for research pertaining to maternal and child health and to the population sciences. As such, the NICHD research program addresses some of the most devastating and costly health problems facing our society. In maternal and child health, these problems include mental retardation, birth defects and genetic disorders, low birth weight and premature infants, pediatric and maternal AIDS, learning disabilities, Sudden Infant Death Syndrome, high risk pregnancy, and childhood accidents and injuries. In the area of the population sciences, research is directed toward developing more effective and safer methods of contraception, evaluating the safety and effectiveness of available methods, devising strategies to help reduce the number of teenage pregnancies, and investigating at the molecular and genetic level the biology of human reproduction.

This broad research program of the NICHD is carried out by scientists working in the Institute's own laboratories as well as by those working under grant or contract support in laboratories, hospitals, and universities around the U.S. and in a few foreign countries. The program encompasses both biomedical and behavioral research and spans the spectrum from highly technical biochemical engineering which may one day lead to treating disease at its genetic or molecular level to observing normal babies at play in order to better understand the processes of human development.

To coordinate and conduct this research, the NICHD is divided into four major areas: the Center for Research for Mothers and Children (CRMC), which studies issues such as prematurity, infant mortality, mental retardation and human learning and behavior; the Center for Population Research (CPR), which studies fertility and infertility, basic reproductive sciences, contraception and population issues; the Intramural Research Program (IRP), which conducts basic and applied research in the Institute's own laboratories; and the Prevention Research Program (PRP), which utilizes the disciplines of epidemiology and biometry to develop new knowledge to be applied to the prevention and reduction of problems associated with human development and coordinates the prevention research activities of the NICHD.

Overall Budget Policy

The 1991 budget request for the National Institute of Child Health and Human Development favors basic research and totals $461,473,000, including $29,010,000 for AIDS research. This amount represents a total increase of $18,567,000 over the comparable FY 1990 estimate, including an increase of $2,261,000 for AIDS research.

The NICHD 1991 budget request for research project grants is $277,683,000, an increase of $13,649,000 above FY 1990. The total number of research project grants awarded in 1991 will be 1,431, a decrease of one grant award below the 1990 level. The request will support 1,069 noncompeting research project grants at an average cost of $190,452 and a downward negotiation rate of approximately 15.5 percent. The average cost of noncompeting research project grants in FY 1990 was $183,012. The number of competing research project grants will be 362 at an average cost of $199,939 and a downward negotiation rate of approximately 12.0 percent. The average cost of competing research project grants in FY 1990 was $185,176.

In research centers, the request provides $36,914,000 for funding 53 centers. The amount and number are the same as 1990.

The amounts in other research grants remain essentially the same and provide funding for the same number of career, small instrumentation, and other research awards. The 1991 request for research training remains essentially the same as the 1990 level and will provide support for 690 research trainees, the same number as in 1990. The amount requested in 1991 for research and development contracts represents an increase of $587,000 above the 1990 level.

In intramural research, the request provides $58,959,000, an increase of $4,199,000. This amount will cover cost increases for centrally furnished services, laboratory supplies and services, animal holding costs, expenses related to the occupation of new laboratory space, and increased costs for salaries and three additional FTEs.

The 1991 request provides $22,808,000 in research management and support, an increase of $1,035,000 over the 1990 level. This amount will cover increases for centrally furnished services, pay-related costs, and other supplies, equipment, and services. In addition, the request will support three new FTEs.

Program Accomplishments

A major study has found that chorionic villus sampling (CVS), a new procedure to test for genetic abnormalities before birth, can be nearly as safe and effective as amniocentesis, a method of prenatal testing in use for two decades. The study found that increased risk of fetal loss associated with CVS is less than 1 percent higher than that associated with amniocentesis. CVS has several advantages over amniocentesis: it can be performed earlier in pregnancy and its findings can be determined almost immediately.

The NICHD funded the nation's first research centers to combine the biomedical and behavioral sciences to focus specifically on learning disabilities. The centers are located at Johns Hopkins University in Baltimore, Maryland and Yale University in New Haven, Connecticut.

Last year, a major laboratory study designed to evaluate the suitability of using condoms and spermicides to prevent the spread of sexually transmitted diseases (STDs) was completed. The results testify that the high quality of the condoms on the American market should provide a substantial degree of protection against STDs.

Also completed last year was a spermicide testing program that compared the inhibitory effects of six spermicides on nine common STDs. All of the spermicides were effective against some of the STDs, although two formulas appeared to have the best overall effectiveness against a spectrum of disease agents.

Another study showed a 60 percent decline in the rate of gonorrheal infection and a 50 percent decline in chlamydia infection in women who used spermicides on a regular basis over a 6-month period.

Previously, NICHD intramural scientists had developed a vaccine that is now in wide use around the world to protect older children from Hemophilus influenzae type b, a bacterium which can cause meningitis in children. This meningitis is the most common cause of acquired mental retardation. Now, these scientists have developed a new Hemophilus influenzae vaccine for young infants. This safety and effectiveness of this new vaccine has been studied in 18-23 month olds and now in 2-3 month old infants. No serious side effects were observed, and protective levels of antibodies were reached in both groups after three injections.

The technique used to produce the new Hemophilus influenzae vaccine has been applied to other bacteria that cause important infectious diseases in humans, including salmonella (the cause of typhoid fever), pneumococcus (the cause of pneumonia), and Shigella dysentariae (the cause of epidemic diarrhea). A similar vaccine has been created which is targeted against Staphylococcus aureus, often a cause of life-threatening infection in burn patients, premature babies, and other hospitalized patients. These vaccines have been successfully tested in animals, and human trials are planned.

The first part of a two-part, Congressionally mandated study of infants fed a chloride-deficient formula is now complete. The findings from this

study suggest that the chloride-deficient formula has not affected the long-term intellectual development of these children.

NICHD scientists have developed a new, safe way to learn how bones use calcium. The technique measures how the body distributes calcium once it is ingested and how rapidly the body uses this mineral. The new method is safer than old methods of tracking calcium in that it requires no radioactivity. Information obtained by this new methodology is already being used to help design diets for premature babies and to find out what is going wrong in the bones of patients with osteoporosis.

A new study has found that vitamin use around the time of conception has no effect on the incidence of neural tube defects such as spina bifida or anencephaly, serious birth defects affecting the central nervous system. This contradicts several recent studies which suggest that a woman who takes vitamins before or shortly after getting pregnant can protect her baby from neural tube defects. However, NICHD researchers who conducted this new study believe that the results of previous studies are questionable because of design and other problems.

NICHD-supported scientists have developed two mouse models for neural tube defects. The models will be used to identify the causes of neural tube defects, one of the most common developmental anomalies of the nervous system.

Coronary artery disease is the leading cause of death the U.S. Evidence is accumulating that atherosclerosis leading to coronary artery disease begins in adolescence or even in childhood. Early detection of this process will pave the way to preventing this disorder later in life. NICHD-supported investigators have recently shown that adolescent boys with excessive accumulation of abdominal fat also have decreased levels of high-density lipoprotein (HDL) cholesterol which serves to protect against the development of coronary atherosclerosis. These results point to adolescent abdominal obesity as an indicator of cardiovascular risk in adulthood. The NICHD plans to follow up these findings with additional research.

NICHD funded research has found that antibodies to sperm may be a factor in repeated miscarriages or low fertility in some women. Antisperm antibodies were found in almost half of the women in the study who miscarried and in nearly 40 percent of those who did not conceive over an 18-month period. Recognizing this as a cause of some infertility cases may lead to treatment and successful childbearing.

Phase II clinical trials of the polyvinyl sponge containing benzalkonium chloride as the spermicide are nearly complete. The sponge has an overall failure rate approximately the same as the cervical cap and the diaphragm. However, user failure rates are lower for the sponge than for the other two methods, supporting the concept that while the both the cap and the diaphragm may be more effective than the sponge when used consistently, the ease of sponge use makes it more attractive to the contraceptive user.

Clinical trials of two chemical analogs of LHRH, a hormone produced in the brain that regulates reproductive processes in both men and women, will be undertaken to ascertain the potential of these drugs for fertility regulation in men.

AIDS Research Program

The number of women and children infected by the human immunodeficiency virus (HIV) is increasing. AIDS is now the sixth leading cause of death in young people from 15 to 20 years of age, and the ninth cause of death among children 1 to 4 years. The AIDS-related research of the NICHD has several major emphases, including the transmission of HIV from mother to child, the effect of the virus on fetal and child development and methods to prevent the onset of AIDS in HIV-positive children, AIDS treatment, methods of preventing the sexual transmission of the AIDS virus, and research into the basic mechanisms underlying the biological activity of HIV.

An integral component of the NICHD AIDS research program is to develop strategies and methods to prevent the sexual transmission of HIV infection. The Institute is supporting a major program of new condom development. The goal is to improve the acceptability and efficacy of these devices, with particular emphasis on developing improved condoms using polymers other than latex rubber.

An extensive program has been under way for several years to quantify the degree to which currently available condoms and spermicides, alone and combined, reduce the risk of sexually transmitted diseases including AIDS.

A major laboratory study was completed recently to evaluate the suitability of using condoms, and condoms plus spermicides, in preventing the transmission of AIDS. The results of the in vitro condom testing program demonstrated that the current supply of condoms on the American market is of high quality and should provide a substantial degree of protection from the human immunodeficiency virus (HIV) that causes AIDS and other sexually transmitted diseases (STDs) that are cofactors for acquiring AIDS.

This study involved additional laboratory experiments on the integrity of condoms as viral shields. Using the electron microscope, it was demonstrated that latex does not have holes or pores that would allow for the passage of viral particles of any size. These experiments were not done with natural lambskin condoms.

It was also found in this study that spermicide with condoms reduce the amount of viable virus leaking from intentionally damaged condoms, supporting the hypothesis that spermicide used in conjunction with condoms offers additional protection against infection with the AIDS virus. The laboratory experiments also showed that all six of the spermicides tested are effective against some of the common STDs. Preliminary laboratory work with the AIDS virus suggested that all of the spermicides would likely inactivate HIV.

This research indicates that most spermicides inactivate cell-free HIV and that nonoxynol-9 is the most viricidal of all the spermicides tested. Further studies will involve the testing of a variety of spermicides, combinations of spermicides, and spermicides in delivery systems for viricidal activity against intracellular and cell-free HIV. Studies will also ascertain the efficacy of spermicides against HIV present in body fluids, including semen, cervical mucus, and vaginal fluid.

Staff of the NICHD contraceptive evaluation program designed a computer model to determine the amount of protection against HIV that is provided by condoms under a variety of assumptions concerning their efficacy. The model was applied to a group of women identified as being least protected against the acquisition of HIV infection. The model demonstrates that for those at low risk of HIV infection (this includes the general non-IV drug-using heterosexual population of the U.S.), the number of HIV infections attributable to condom failure will be very small and that many more infections will be prevented by the proper use of condoms than can be attributed to their failure. These results provide assurance that condoms can be recommended as protection from HIV infection for those at low risk, even in the absence of quantitative data about condom efficacy. For those at high risk of acquiring HIV infection (e.g., those with partners known to be infected), the uncertainty about the exact efficacy of condoms makes their use problematic. Avoidance of high-risk sexual activity by these people is the only way to assure protection from this disease.

Concern about AIDS has resulted in the focusing of longstanding research efforts in the areas of sexual behavior, sexual transmission of diseases, and contraceptive practice to better address issues specific to the prevention and control of HIV infection. Two research projects have successfully developed protocols for the study of behaviors related to risks of unwanted pregnancy and STDs, including HIV. These studies would lead to national data bases which will provide estimates of the levels of sexual risk behaviors. One of the studies, which focuses on adolescents, would integrate the findings from much of the past research on sexual and contraceptive behavior and provide a national data base on which many hypotheses could be tested.

Data is now available from the second year of a three-year project on contraceptive decision-making by adolescent female clients of an inner-city family planning clinic. Due to early initiation of sexual activity, multiple sex partners, and use of illicit drugs, these young women are regarded as being at increased risk of HIV infection. Preliminary results show that subjects' AIDS knowledge levels (including knowing that condoms are effective in preventing the spread of the disease) are high and that over half perceive themselves to be at some risk of getting acquired immunodeficiency syndrome (AIDS). However, neither knowledge levels nor perceived risk appears to affect use of condoms. The researchers did find that teens who say they are able to talk with partners about condom use are more likely to actually report having used a condom at last intercourse. This suggests that adolescent females can be effective in influencing their partners to use condoms and that they could benefit from assistance in learning the assertiveness and negotiation skills necessary to protect themselves.

Eight research projects recently have been funded that were proposed in response to a request for applications (RFA) entitled, "Behavioral Research on the Use of Condoms to Prevent AIDS." The purpose of this RFA was to solicit research to identify factors affecting the use of condoms. Although many couples have used condoms, only 10 percent of the sexually active women responding to the 1982 National Survey of Family Growth said that their partners were currently using this method. The proportions were lowest among those with lower incomes and lower educational attainment, groups that include a disproportionate number exposed to the risk of HIV infection. Since condoms are one of the primary methods available for controlling the transmission of

STDs, including HIV infection, research into the behaviors and attitudes concerning their use is critical.

The topics with which the eight research projects will be concerned include the following: 1) Determining prevalence, trends, and factors affecting the use of condoms in high-risk patients aged 14-35 attending STD clinics in an urban area; 2) Assessing the attitudes, beliefs, and behaviors of two ethnic groups regarding condom use; 3) Understanding the decision to use condoms among members of three high-risk groups for STDs and AIDS; 4) Examining factors affecting condom use through a follow-up survey of young men; 5) Investigating factors affecting the use of condoms by adult men to prevent AIDS; 6) Studying condom use in a high-risk population; 7) Determining the characteristics of preferred condoms; and 8) Analyzing data from a previous survey concerning factors associated with condom use.

Research is ongoing to develop better treatments for HIV infected infants and children. The NICHD has continued to investigate the role of intravenous immunoglobulin (IVIG) in preventing bacterial infection in HIV positive children. The trial is being conducted in 30 hospitals around the country and has enrolled more than 330 children. The compliance rate of children, parents, or caretakers in adhering to the follow up schedule has been excellent and demonstrated convincingly that community based hospitals in a variety of settings and in different parts of the country, including Puerto Rico, in addition to academic institutions, can implement and conduct complex clinical protocols of clinical trials with HIV infection. This demonstration is of great importance in view of the fact that many HIV infected children are under the care of community based hospitals and not major academic institutions.

To provide an optimal research and treatment assessment system, the NICHD pediatric AIDS clinical trials network will be joined with the pediatric AIDS network supported by the National Institute of Allergy and Infectious Diseases (NIAID) The NICHD supports 28 pediatric AIDS centers which serve the majority of HIV-infected children in the U.S. By the union of the two currently separate networks, the NICHD and the NIAID will conduct clinical trials in anti-retroviral and other therapies in mothers, infants, and children throughout the U.S. Through this unified network, the vast majority of HIV-infected children and pregnant women will have access to clinical trials and to state-of-the-art research and care.

The NICHD also continues to study the effect of HIV infection on hemophiliac children who became infected through contaminated blood and blood factor replacement products. Preliminary data from this study suggest that an unexpectedly high rate of neuropsychological and neuroradiologic abnormalities may be found in the affected children. It is likely that both the hemophilia and the HIV infection may independently contribute to disability in these children. These very early results await further data collection and analysis, but they raise significant concerns for both hemophiliac children and HIV-infected children.

The NICHD has recently funded six investigators around the country who will systematically study the problems of early diagnosis of HIV infection in newborns and infants. Other areas slated for future research activity include the role of the placenta as a conduit for therapeutic drugs and studies focussed on interrupting the transmission of HIV infection from mother to

child; studies of HIV infection and disease in adolescents; improving methods to diagnose HIV infection in neonates and infants; and evaluating community-based, family centered models of care for families affected by HIV.

Research into the biological mechanisms of HIV has been ongoing in the NICHD intramural research program. One area of interest is trying to elucidate the cause of the dementia often associated with AIDS. Previous work by NICHD intramural investigators has suggested that brain cells are killed indirectly by gp120, the external envelope protein of the human immunodeficiency virus (HIV), and that this neuronal death may occur by interference with endogenous neurotrophic substances which normally nurture brain cells, such as a hormone called VIP. Recent work confirms that in fact, gp120 does not act directly on brain cells, but rather, it interacts with the supporting cells of the nervous system which normally produce vital neurotrophic substances. Furthermore, a neuronal survival assay has been used to detect neurotoxic material in the cerebrospinal fluid (CSF) from AIDS patients with dementia. All of the toxicity associated with the spinal fluid of these patients has been shown to be attenuated by a drug, peptide T, which is related to the endogenous neurotrophin, VIP. Monoclonal antibodies to CD4, the receptor by which HIV gains entry to cells, are also specifically effective in neutralizing the neurotoxic material present in the CSF of patients with AIDS dementia. These results improve our understanding of AIDS dementia and also suggest possible therapeutic approaches to its amelioration.

NICHD scientists have studied the synthesis and processing of the HIV envelope precursor glycoprotein, gp160, in an infected $CD4^+$ lymphocytic cell line. This research is directed toward identifying a vulnerable site in the life cycle of HIV that may be amenable to antiviral therapy. This research has shown some promising results and is yielding some interesting and valuable insights into the biological activity of HIV and its components.

National Institute of Child Health and Human Development

Research for Mothers and Children

Authorization: Indefinite

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$237,742,000	$247,241,000	+$9,499,000

Purpose and Method of Operations

The Center for Research for Mothers and Children (CRMC) is the primary extramural program supporting research for maternal and child health at the NICHD and at the NIH. Much of the CRMC research program is directed at preventing prematurity and low birth weight--conditions which account for the majority of the infant deaths in this country each year. Other CRMC research programs are focused on preventing or ameliorating birth defects, mental retardation, and other conditions which inhibit optimal physical or behavioral development. Researchers supported by the CRMC are also studying normal growth and development to better understand these processes. Knowledge gained from these studies is used to develop interventions designed to improve language, reading, and other cognitive skills in children with learning disabilities or mental retardation and to treat various disorders which impair normal physical growth and development.

Rationale for the Budget Request

The 1991 budget request is $247,241,000, an increase of $9,499,000 over the 1990 level. The following are the program plans for 1991.

Birth Defects and Infant Mortality

Current data indicate that birth defects are the leading cause of death in infants under one year of age. A recent study indicates that 20.5 percent of the approximately 39,000 infants who die in the first year of life do so due to birth defects. To effectively reduce this nation's infant mortality rate, a greater emphasis will be placed on research to define the mechanisms resulting in these developmental errors. New technology allows investigations of developmental processes that never before have been explored. Causative mutant genes and their corresponding gene products are now being identified and their biological significance pursued.

Human birth defects are being successfully studied in animal models. Congenital enlarged colon accounts for 33 percent of all neonatal intestinal obstructions and is being explored in animal models for the genetic defect causing the lack of functional innervation. NICHD has developed two mouse

models for neural tube defects, one of the most common developmental anomalies of the nervous system. These models will be characterized to identify causative mechanisms. Hereditary immunodeficiency diseases contribute to infant mortality by impairing the immune response of the infant to infectious agents. Understanding of the expression and regulation of the involved genes as well as studies of normal development of the immune system in utero and post-natally are improving diagnosis and therapy. Cytomegalovirus is the leading cause of congenital infections in this country causing a high incidence of morbidity and mortality. Studies of viral transmission and clinical trials of a vaccine are under way.

Existing methodology holds the promise of fruitful exploration of these etiologic factors with application to amelioration and prevention of birth defects. Understanding the mechanisms regulating development is a viable and realistic goal through application of our current research capabilities and basic biologic knowledge.

Preventing Low Birthweight

A current major study is designed to ascertain nutritional and other factors that account for the high rates of low birthweight among urban blacks. Nationwide figures for low birthweight are 12.5 percent for black and 5.7 percent for white babies. However, the rate for black babies in Washington, D.C., is 18 percent, and at Howard University Hospital it reaches 20.6 percent. Scientists have made some startling findings in a group of 680 pregnant black women living in Washington, D.C.: about 20 percent of them failed to gain the minimum recommended amount of 21 pounds during pregnancy; 46 percent of them have levels of serum ferritin below the normal range, and 30 percent of them have serum folate below the normal range. These nutritional findings are important because infant birthweight correlates significantly with folate intake during the second trimester of pregnancy. One of the most remarkable findings of this project is that the rate of low birthweight in the study population, identified before the 26th week of pregnancy, has dropped to 8.9 percent while the general rate for those delivering in the same hospitals is over 20 percent. Attention is now being turned toward delineating the differences between these women and those in a group who came under observation later in pregnancy, in whom the rate of low birthweight remains high. For the near future, intervention studies are being planned to test specific factors in the study which might account for this improvement.

Sudden Infant Death Syndrome (SIDS)

The NICHD has identified two major initiatives for research on SIDS in FY 1991. These are part of a five-year research plan that was submitted to the United States Senate last year. The first initiative is to establish a network of clinical sites which will study the maturation of cardiorespiratory control during the critical period in infants at risk for SIDS. These studies will investigate the physiological significance of apnea monitoring to illuminate its role in preventing SIDS. The second initiative is to develop animal models that test specific hypotheses regarding the cause of SIDS and that can be used for preclinical studies of preventive interventions. Animal models are useful to perform the necessary developmental studies to understand the pathogenic mechanism of SIDS, since it is possible to alter the in utero

and postnatal environment. The criteria for the animal models will be developed in conjunction with scientists convened for a workshop in FY 1990.

Clarification of the pattern of maturation of fetal breathing is one step toward an understanding of respiratory problems in the neonate and the development of appropriate preventive measures. In a baboon model, it has been shown that sequential, developmental patterns can be defined which may reflect development of fetal lung and the maturation of central nervous system processes regulating the organization of breathing activity. Studies to assess fetal breathing in the human are feasible and anticipated in FY 1991. Such studies may lead to the prediction of breathing dysfunction in infants, and ultimately to the prevention of potentially fatal disorders.

Child Health Research Centers

The NICHD will initiate a new program of Child Health Research Centers intended to provide resources to speed the transfer of knowledge gained through studies in basic science to clinical applications which will benefit the health of children. In these Centers, each of which will focus on a specific area of basic science applicable to pediatric problems, established investigators will make available their expertise and laboratory facilities to junior investigators who are developing the research skills and preliminary data needed to initiate competitively funded new research projects. A shared core laboratory will augment each Center's technical capabilities. It is anticipated that five or six Centers will be funded in FY 1990, and that the program will be continued in FY 1991.

Mental Retardation

In 1966, the NICHD initiated, through money authorized under Public Law 88-164, the establishment of Mental Retardation Research Centers. These centers provide support for research and research training relevant to mental retardation and other developmental disabilities. The efforts of these Centers have provided much of the empirical basis for the advances in fundamental knowledge of the many causes of mental retardation, in the prevention of a wide variety of developmental disabilities, and in improving the function of those who are developmentally disabled.

A recent CRMC-supported study of mortality and morbidity for individuals with mental retardation found differences in those who lived with a family, in skilled nursing homes, or in institutions. Deinstitutionalized individuals with mental retardation who were placed in a skilled nursing facility had higher mortality rates. For older individuals with mental retardation, increased mortality was found and attributed, in part, to immobility, lack of toileting skills, and eating dependency. In FY 1991 we expect further information on this topic.

Down syndrome is the most common genetic birth defect associated with severe physical and mental impairment expressed throughout the life span. In June 1989, NICHD sponsored a workshop on "Progress toward mapping human chromosome 21 and mouse chromosome 16." The participants concluded that mapping these two chromosomes, which share several genetically homologous regions, is progressing very rapidly. It was felt that mapping these two

chromosomes is serving as the prototype for the human genome initiative which will be supported in FY 1990 and FY 1991.

Rett Syndrome

Rett syndrome is a neurodegenerative disease that has been found only in females who are apparently normal until 6 to 12 months when abnormalities of motor and cognitive abilities emerge. Currently funded research has found abnormalities in both the neurochemistry and neuroanatomy of children with Rett syndrome. Specifically, the structure of the caudate nucleus is abnormal, the gross size of the brain is significantly less than normal, and the basal ganglia are smaller than normal. The glucose metabolism is aberrantly low in the temporal and parietal lobes of the brain. Behavioral modification techniques have proved to be effective in reducing hand wringing, improving functional hand use, and improving sleep patterns.

Additional research on Rett syndrome will focus on finding the cause of this syndrome, describing the course of the abnormality during development, and developing interventions to ameliorate the functional losses that characterize these young girls.

Infant Day Care

Over five million infants and toddlers under the age of three require some form of day care while their parents work. This remarkable statistic is correlated with an unprecedented increase in labor force participation of mothers with young children during the past decade. To address the many questions of parents and relevant institutions in the private and public sectors concerning the consequences of day care beginning in infancy, the NICHD has funded a multi-site consortium consisting of 10 teams of investigators who are using a common protocol to examine the development of children who have varying child care experiences. These range from exclusive maternal care to extensive reliance on day care during the first three years of life. The aspects of development that will be studied encompass social, emotional, language, and cognitive outcomes.

Learning Disabilities

In FY 1989, the NICHD funded two new interdisciplinary centers that focus upon discovering the behavioral and biological causes of learning disabilities. NICHD plans to fund an additional such center in FY 1990. Results from currently funded programs in dyslexia (reading disability) reveal strong evidence for the existence of a chromosomal anomaly being linked to one or more forms of learning disability. Research sponsored by the Institute has also demonstrated that computer-aided instruction is a useful approach for remediating some dyslexics. The Institute will sponsor four scientific meetings on learning disabilities, two of which will be co-sponsored by major learning disability societies. Such meetings will bring the concerns of the learning disabled and their parents to the NICHD-funded scientists who conduct research on this topic.

Childhood Injury

Childhood injuries are the major cause of death and disability in children after the first year of life. To help address this great threat to our Nation's children, NICHD has initiated a multifaceted research program to elucidate mechanisms that are causally related to risk and safety behaviors. The program has funded a diversity of unique studies (15 in number). One such study is investigating the contribution of developmental factors to the likelihood of pedestrian injury. The new knowledge gained can help guide more effective interventions for supervising of child pedestrian behavior.

Atherosclerosis

Coronary artery disease is the leading cause of death in this country. Evidence is accumulating that atherosclerosis leading to coronary artery disease begins in adolescence and in some cases in childhood. Early detection of this process will pave the way to preventing the ravages of this serious disorder later in life. NICHD-supported investigators have recently shown that adolescent boys with excessive accumulation of abdominal fat also have decreased levels of high-density lipoprotein (HDL) cholesterol which serves to protect against the development of coronary atherosclerosis. These results point to adolescent abdominal obesity as an indicator of cardiovascular risk in adulthood. The Institute is now soliciting applications to identify genetic and biochemical markers which predict the development of the adolescent and adult obesity which so frequently is a precursor of coronary artery disease. Other NICHD-supported investigators have shown that adolescent boys from families prone to coronary artery disease have elevated levels of low density lipoprotein (LDL) cholesterol, apolipoprotein B, estradiol and dehydroepiandrosterone sulfate (DHEAS). These important findings parallel those in men who have heart attacks before age 55. Measurement of these serum factors in adolescence may now serve as new markers for increased risk of coronary artery disease later in life. Development of these new markers is critical to mounting an intensive intervention effort in childhood and adolescence aimed at preventing coronary atherosclerosis.

Inborn Errors of Metabolism

Nutritional therapy remains one of the main approaches to the management of inborn errors of metabolism, but it has been only marginally successful because existing formulas are either unpalatable or have unpleasant odors. To address this problem, the NICHD solicited research grant applications for studies to improve the effectiveness of currently used nutritional therapies by making them safer and more palatable, and to develop new rational dietary therapies. Four research grant applications were funded in FY 1990 designed to improve dietary management of phenylketonuria, galactosemia, adrenoleukodystrophy, and metabolic disorders that are associated with increased blood levels of ammonia which is toxic to the brain. These projects should begin to provide needed information in FY 1991.

National Institute of Child Health and Human Development

Population

Authorization: Indefinite

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$127,677,000	$132,465,000	+$4,788,000

Purpose and Methods of Operation

The NICHD's Center for Population Research (CPR) is responsible for the primary Federal extramural effort in population research. CPR carries out its programs through the support of research and research training in the biomedical, demographic and behavioral sciences. Funding is provided through grants and contracts for fundamental biomedical research in the reproductive sciences relevant to problems of human fertility and infertility, the development of safe and effective methods for fertility regulation, the evaluation of the benefits and risks of current contraceptive methods, and demographic and behavioral sciences research on the causes and consequences of population structure and change.

Rationale for the Budget Request

The 1991 request is $132,465,000, an increase of $4,788,000 over the 1990 level. The following are program plans for 1991.

Reproductive Sciences

The program in the reproductive sciences supports basic science research to facilitate advances in our knowledge of reproduction which will expand our understanding of fertility regulating mechenisms and provide new approaches for alleviating or curing infertility or reproductive diseases or disorders. This involves research in the areas of reproductive medicine, reproductive genetics and immunology, reproductive endocrinology, developmental biology of reproduction, and reproductive biology.

An NICHD-supported scientist has recently studied 109 infertile couples with respect to a possible relationship between the presence of sperm antibodies and either diminished conceptions or increased miscarriages. Each couple was characterized with regard to pregnancy outcome over an 18-month period through the use of an assay to detect antisperm antibodies in the individual's serum. It was found that antisperm antibodies were present in the sera of 38.2 percent of the women who did not conceive and in 43.8 percent of the women who miscarried. In contrast, antisperm antibodies were only found in 11.8 percent of the women with successful pregnancies. These results

suggest that the presence of antisperm antibodies in female sera correspond to a lowered probability of attaining a successful pregnancy due to an increased incidence of conception failures or early (first trimester) miscarriages.

Research supported in the area of reproductive medicine, aimed at the solution of problems of human infertility and reproductive disorders, will include studies concerning diagnosis, mechanisms, treatment, and prevention of infertility, endometriosis, polycystic ovarian syndrome, and reproductive consequences of infections, including sexually transmitted diseases. Reproductive genetics and immunology studies will focus on the genetic basis of fertility and reproductive disorders, immunologic infertility, and the potential of immunocontraception. Reproductive endocrinology research will emphasize neuroendocrinology, pituitary, gonad, genital tract, hormone action mechanism, and blastocyst implantation. Studies concerning the developmental biology of reproduction will involve the use of the most advanced biophysical and biochemical techniques of cell biology and cell physiology on oogenesis, fertilization, and preimplantation embryos to study the more readily visible results of gene activity. Reproductive biology studies will include continued active exploration of the regulatory and modulatory roles of the various growth factors involved in reproductive processes.

Contraceptive Development

The contraceptive development program supports clinical trials and laboratory studies aimed at developing and improving methods of fertility regulation, for both men and women, that are safe, effective, reversible, and acceptable to various population groups. Research goals include the development of new drugs to regulate fertility in both sexes, the development of improved methods of drug administration, the improvement of barrier methods of contraception, and the provision of research resources.

An investigator funded by NICHD is completing the Phase II clinical study of the polyvinyl sponge containing benzalkonium chloride as the spermicide. In terms of contraceptive efficacy, the sponge has a failure rate approximately the same as the cervical cap and the diaphragm. Preliminary life table analysis indicates a failure rate of 9.7 percent at six months of use and 17 percent at twelve months. Separation of the overall failure rate into its method and user failure components reveals a significant difference between sponge and cervical cap or diaphragm users. Over half of the matched sponge pregnancy rate is attributable to method failure. With the cervical cap or diaphragm pregnancy rate, only one-third is due to method failure. Conversely, user failure rates are lower for the sponge than for the cervical cap or diaphragm. These data support the concept that while both the cap and the diaphragm may be more effective than the sponge when used consistently, the ease of sponge insertion makes it more attractive to the contraceptive user.

Research to be supported through the contraceptive development program will include clinical trials of two analogs (chemical copies) of luteinizing hormone-releasing hormone (LHRH), a hormone produced in the brain that regulates reproductive processes in both men and women, to ascertain the potential of these drugs for fertility regulation in men. Phase II clinical studies of one of these analogs, "Nal-Glu," will be completed in male volunteers. Clinical trials will be initiated in male volunteers with the

analog, Antide, and after the toxicological evaluation is satisfactorily completed long-term studies will be implemented. Clinical studies of modified Capronor subcutaneous implant devices which release the contraceptive steroid, levonorgestrel, will be initiated. Clinical trials with new long-acting injectable progestin and androgen also will be started. Clinical studies with new transdermal patches will be continued and research on additional new patches will be solicited. With regard to barrier methods of contraception, new disposable diaphragms and new spermicidal formulations will be evaluated, research on the development of new spermicides will be supported, and studies of new condoms for both the male and the female, involving new condom materials and designs, will be initiated in view of their vital role both in contraception and in deterring the spread of sexually transmitted diseases.

Contraceptive Evaluation

The contraceptive evaluation program designs and supports clinical, epidemiological, and basic science studies to elucidate the safety and efficacy of fertility regulation and of all gynecological treatments and surgical procedures. A major emphasis of the program is to demonstrate the degree to which barrier contraceptives reduce the risk of gonorrhea, chlamydia, herpes, and other viral infections, including AIDS.

An NICHD-supported researcher at Group Health Cooperative of Puget Sound (GHC) in Seattle, Washington, has recently completed a retrospective cohort study of the sequelae of tubal sterilization. The cases included 8,560 women aged 20-49 who had a tubal sterilization at GHC between 1968 and 1983. These women were compared to nearly 26,000 non-sterilized women who were matched at a 4:1 ratio on the basis of birth year and year of first enrollment in the GHC health plan. A second comparison group of 4,155 wives of sterilized men, identified by GHC automated enrollment files, was used to control for factors associated with a couple's decision to permanently and surgically terminate childbearing potential. The researcher found an overall elevation in the risk of having a hysterectomy following tubal sterilization (relative risk=1.58), with the relative risk rising to 3.4 for women who were sterilized at ages 20-29. A plausible explanation for this risk in younger women is that when a woman has uterine pathology which might require a hysterectomy, the physician would probably attempt to preserve her reproductive capability, while a physician might decide in favor of the hysterectomy in a woman with a prior tubal sterilization. Additional findings show an elevation in dilation and curettage and menstrual disturbances, particularly in women sterilized in the 20-29 age group. Sterilized women had a higher risk of pelvic inflammatory disease and also had a significantly higher rate of hospital admissions. There was no evidence of an increase in breast cancer, endometrial cancer, endometriosis, cardiovascular or cerebrovascular disease. The mortality experience of the sterilized women also was no different from that of either comparison cohort.

The contraceptive evaluation program will continue supporting the assessment of steroid hormone contraceptives, including continued investigation into the association between reproductive system cancer and long-term exposure to currently marketed contraceptive steroids, with particular attention to the risk in women with additional cancer risk factors and with special emphasis given to young women. The benefits of contraceptive

steroids, including the putative protective effect vis-a-vis rheumatoid arthritis, systemic lupus erythematosus, genitourinary diseases, toxic shock syndrome, and many other reported benefits, will continue to be evaluated. The monitoring of current oral contraceptive users for short-term side effects according to various pill formulations, such as the role of the pill in ameliorating or worsening premenstrual syndrome, will be supported. Research will be directed at understanding the relative safety and quantifying the failure rates of the established and newly emerging procedures used for female sterilization, and ascertaining the long-term health effects of female sterilization. Surveillance using vital statistics will quantify the findings that men who are vasectomized have a longer life expectancy. Clinical studies will be supported to compare the efficacy of various methods for the reversal of male and female sterilization procedures. The use-effectiveness of various barrier methods, including the new contraceptive sponge, will continue to be evaluated. Studies will be supported to ascertain and quantify the reduction in the risk of bacterial and viral sexually transmitted diseases (STDs) and pelvic inflammatory disease among women who use barrier methods of contraception. In vitro studies will be aimed at determining the maximally inhibitory spermicides against viral STD pathogens, including hepatitis and the human immunodeficiency virus.

Demographic and Behavioral Sciences

The demographic and behavioral sciences program focuses on the size, rate of growth, and composition of our Nation's most valuable asset, its population. The topics addressed by specific research projects derive from fundamental questions concerning the growth and distribution of our population, and their relation to individual and societal welfare. The program's strategy concentrates on the questions of basic scientific concern and current societal importance.

The investigator of an NICHD-supported study of the effectiveness of sexuality education programs has reported the findings a year after teenagers, aged 15-17, had either of two programs (an experimental one or a more traditional one) and compares their behavior to that of teenagers who did not have either program. Teenagers participating in the programs were no more and no less likely to have had sexual intercourse in the intervening year than were those who had not participated in any program. However, for both males and females who did have intercourse, there were significant increases in contraceptive use among those who had been exposed to either sexuality education program.

Research in the demographic and behavioral sciences will continue to focus on the high rate of unintended pregnancy among American women. The problems associated with adolescent pregnancy and childbearing will be examined further in order to increase our understanding of adolescent behavior in this area. Research will continue to be supported on fertility trends and their relation to other demographic, social, and economic processes in the United States, such as the relationship of major changes in the marital behavior of Americans to fertility behavior and the family experiences of children. The National Surveys of Family Growth and the National Longitudinal Survey - Youth Cohort, both partially supported by NICHD, provide an important data resource for analyzing fertility trends. In addition, research will proceed on the use of condoms to prevent AIDS, and on the relationships between STDs and fertility-

related behavior. Studies will be supported to examine attitudes and behaviors about the desirability of bearing children biologically related to both parents, with particular relevance to the new technologies for infertility treatment, and about the costs of treating infertility. Research on intergenerational family relationships will continue to be funded on such topics as the effect of family disruptions on child socialization, the effect of parental employment on child development, and intergenerational transmission of attitudes and values. Studies concerning child care and fertility will examine the role of cost and availability of child care on the employment-fertility relationship. Research will continue to be supported dealing with migration, in order to understand better this most dynamic force shaping the population structure of American communities. Studies in the areas of mortality, the determinants of low birth weight, and child health, such as on racial and ethnic differentials in low birth weight, will also continue to be funded.

National Institute of Child Health and Human Development

Intramural Research

Authorization: Indefinite

Budget Authority:

1990 Appropriation		1991 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA
261	$54,757,000	264	$58,959,000	+3	+$4,202,000

Purpose and Method of Operations

The mission of the NICHD Intramural Research Program is to conduct research on the biomedical and behavioral aspects of human development. This research includes studies on reproduction; on the factors that prevent normal development, and as a consequence, set the stage for birth defects and later diseases; and epidemiologic investigation in the areas of great importance to the public health. The program emphasizes studies in animals that serve as models for human development, as well as clinical studies in humans of genetic diseases and inborn errors of metabolism, congenital malformations, and endocrine and metabolic disturbances. The program also makes a significant contribution to the future prevention of developmental disorders through the research training it offers to young clinical and basic research scientists.

The Prevention Research Program is multifaceted, comprising both intramural and extramural activities, and is responsible for the coordination of the Institute's programs related to health promotion and the prevention of disease, disability, and handicapping conditions. The program assures high priority focus in the Institute on prevention research in areas related to maternal and child health, reproduction, and population dynamics, and fosters the maintenance and enhancement of health and well-being by transferring knowledge gained through prevention research to health care professionals and the lay public.

Rationale for the Budget Request

The 1991 request is $58,959,000, an increase of $4,202,000 over the 1990 level. This amount will cover built-in increases of $3,712,000 for centrally furnished services, laboratory supplies and services, certain animal holding costs, and pay-related costs. The program increase of $490,000 will provide for expenses related to the occupation of new laboratory space, other animal holding costs, and salary and pay-related expenses for three additional FTEs.

Laboratory and Clinical Research

Intramural scientists will continue to pursue promising leads that are broadly concerned with the biological and neurobiological, medical and behavioral aspects of normal and abnormal human development. The program's goal is to probe deeply into all of the life processes as a basis for maintaining health. This goal reflects the belief that the key to the prevention of common "adult" diseases, such as cancer, heart disease, mental illness, and premature aging, lies in our understanding of the rules which govern early development. Research is carried out in patients as well as in a diversity of animal models. Currently, two themes of basic investigation are being emphasized throughout the program: The structure, function, and transmission of genes (knowledge in this area is critical as we embark upon an era of "gene therapy"), and "signal transduction," the complex pathway by which hormones, neurotransmitters, antigens, and drugs induce a signal at the cell surface which eventuates in the expression of genes in the nucleus. There is also an intensive effort in vaccine development, particularly with respect to common but serious bacterial infections of children; a major emphasis on the development of new methods and tools of interest to biotechnology; a substantial investigation of the molecular basis of brain function in the developing organism; and a special focus on cellular and molecular biologic aspects of HIV infection.

Neurobiology: Experience Influences Brain Structure

One of the most striking features of the nervous system is the formation of orderly connections between nerve cells during normal development, but how this orderliness is achieved has been enigmatic. NICHD neurobiologists believe that electrical signals between the nerve cells might affect their physical connections and to address this question, they have grown two kinds of nerve cells in a specially designed apparatus. These investigators have succeeded in isolating and growing part of the circuitry of the developing nervous system in the laboratory. Scientists believe that at least some forms of mental illness may be due to a disturbance in the orderly formation of nerve cell connections. For example, neurologists have found disordered relationships between nerve cells in the brains of autistic children, and patients with Alzheimer's disease also appear to have a disruption in the orderly connections of the brain. The brain generates its own electrical activity, and this laboratory model reflects that kind of stimulation. However, the developing brain is exposed to other kinds of stimuli as well, which collectively comprise experience; this notion of experience influencing the actual structure of the brain appears to have enormous societal and biological importance.

Neurobiology: Probing the Infant Mind for the Roots of Intelligence

Through the ages, psychologists have debated whether intelligence is inherited or derives from experience. This question could be addressed if a reliable test of IQ could be devised with which to examine the capacities of the infant mind. NICHD researchers have now shown that a strong inference can be made as to native intelligence in the infant by measuring how long something holds an infant's attention. An alert young infant will typically pay attention to an environmental stimulus when that stimulus first appears. If the same stimulus remains available to view, the infant pays less and less

attention to it. This decline in attention is called habituation. Habituation is typically measured by observing how long pictures projected onto a screen can hold a baby's attention. These investigators have found, in carefully controlled and longitudinal studies, that to a large extent, one can predict how well older children will perform on certain tests of mental ability from how efficiently they habituate as infants. It is as if a bright infant can process information quickly and move on to other stimuli. However, certain aspects of mothers' interactions with their infants are also strongly predictive of mental ability. In particular, mothers who consistently draw their babies' attention to their surroundings appear to produce more intelligent children. Interestingly, infants who habituate faster tend to encourage their mother's attention. Thus, it may be that babies who process information efficiently excite their environment in ways that promote their own development. These results may be valuable in allowing us to identify what environmental factors facilitate a child's living up to his intellectual potential, and what factors inhibit potential. Moreover, the results point the way toward techniques that parents and other caregivers might use to help their children develop verbal and related thinking skills. Such techniques may be particularly helpful to the increasing numbers of children being reared in day care centers, where there are fewer opportunities for one-to-one interaction, and to their working parents, who may have less time to spend with them.

Neurobiology: Glycine Allows the NMDA Receptor to Remain Sensitive to Glutamate

Many nerve cells in the brain use glutamate, in minute, carefully controlled amounts, to transmit signals to other nerve cells. The recipient nerve cells have special proteins-- NMDA receptors--on their surfaces that recognize glutamate, a naturally occurring amino acid. NMDA receptors are currently the subject of intensive study in many laboratories because it is widely believed that they may hold the key to how we learn and remember. NMDA receptors are also of great interest because they appear to hold the key to how the brain is damaged when deprived of oxygen, for example, during a stroke, heart attack, or difficult childbirth. In these situations, nerve cells lose the ability to control the flow of glutamate, and excess glutamate causes irreparable damage to those nerve cells that bear the NMDA receptors. NICHD neurobiologists have found that once NMDA receptors are occupied by glutamate, they change shape. This opens up minute channels within the receptor protein, allowing ions to flow in and out of the nerve cells which causes them to become excited. However, it has been known that if the nerve cell is bathed continuously in glutamate, it tires and its response wanes. These investigators have now shown that another naturally occurring amino acid, glycine, allows the NMDA receptor to remain sensitive to glutamate. Once glutamate is bound to the NMDA receptor, glycine keeps this complex protein in the right shape to conduct ions in and out of the ion channel, which keeps the nerve cell active. Understanding exactly how the NMDA receptor works may allow researchers to design drugs to block the harmful effects of glutamate. Blocking the action of glycine is one approach that might be used to prevent excessive activation of NMDA receptors, and novel drugs acting at the glycine binding site now seem a real possibility for a new therapeutic approach to preventing brain damage after strokes or other situations that cut off the flow of oxygen.

Biotechnology: Control of Gene Expression by Iron

Cells are acutely sensitive to iron--with either too much or too little they can't survive. By studying how cells balance their iron levels, NICHD researchers have discovered a novel biological switching mechanism within the cell. These scientists have found a unique cellular protein that can sense how much iron the cell contains. This protein responds to fluctuating iron levels in the cell by changing its shape. When iron levels go over the safe limit, the protein becomes compact; when they fall too low, the protein opens up. This research has wide significance beyond explaining how iron levels are balanced. This is because it is usually the shape of proteins that determines how they function. Thus, the type of switching mechanism revealed by the iron-sensing protein is very likely to be a common way that cells control many biological processes, including the expression of other genes. These scientists have also found that when iron-responsive elements (IREs) are fused to any gene experimentally, they make that gene's expression exclusively dependent upon the level of iron in the cell that contains the injected gene. Thus, IREs are proving to be of great utility to the biotechnology industry, which has long sought a way to regulate gene expression with this degree of precision.

Biotechnology: Use of the Mass Spectrometer to Measure How the Body Uses Calcium

NICHD scientists have developed a new, safe way to learn how bones use calcium, and thus more about how children grow and how aging bones become brittle. The technique, which relies on a machine called a mass spectrometer and some simple math, measures how the body distributes calcium, once it is ingested, and how rapidly the body uses this mineral. But the new method differs from other tracking methods in that it requires no radioactivity to locate the calcium, which makes it much safer. Information gathered by the mass spectrometer is already being used to help design diets for premature babies, who need extra calcium, and to find out what is going wrong in the bones of older patients with osteoporosis.

Clinical Trials: New Approaches to the Treatment of Short Stature

NICHD intramural scientists are examining various ways to treat the many children who have short stature, but no apparent deficiency of growth hormone. The first approach tests the hypothesis that prolonging the growth period by delaying puberty can enhance adult height. The observation that patients with pubertal delay due to hypogonadism are significantly taller than normal subjects provides support for this hypothesis. This clinical trial utilizes recently developed hormone analogues which are able to retard pubertal development. A second clinical trial tests the hypothesis that supplemental growth hormone will increase the adult height of children with non-growth hormone deficient short stature ("constitutional," "familial," or "idiopathic" short stature). This trial will meet an important societal need for objective outcome data upon which to make rational risk/benefit analyses concerning this new treatment approach. The number of short children in the United States who are potential candidates for growth hormone treatment is one million; growth hormone, as produced from recombinant DNA, is now readily available but

costly. Thus, the answers sought by this trial have important clinical, economic and regulatory, as well as scientific, significance.

Vaccine Development: Haemophilus Influenzae Conjugate Vaccine

Haemophilus influenzae type b is a bacterium which can cause meningitis in children, and this meningitis is the most common cause of acquired mental retardation. NICHD investigators pioneered the development of a Haemophilus influenzae (H. flu) type b vaccine, now in wide use throughout the world. While very effective in children, the vaccine has not been effective in young infants due to the immaturity of their immune systems and their inadequate response to relatively weak antigens such as those of H. flu. However, it is in infancy that the highest attack rate of Haemophilus influenzae occurs. These scientists have now devised a new H. flu vaccine that binds the organism's capsular polysaccharides (the bacterium's antigenic domain) to carrier proteins, which increases the immunogenicity of these protective antigens as well as their booster effect. The safety and immunologic properties of the new vaccine were investigated in 18-23 month olds and now in 2-3 month old infants. Protective levels of antibody were reached in both age groups after three injections, and antibody levels remained as high one year following the injection as after the naturally occurring infection. The concept of conjugating bacterial polysaccharide antigens to carrier proteins in order to enhance their immunogenicity has also been applied to other bacteria that cause important infectious diseases in humans, including salmonella (the cause of typhoid fever), pneumococcus (the cause of pneumonia), and Shigella dysentariae (the cause of epidemic diarrhea). A similar vaccine has been created which is targeted against Staphylococcus aureus, often a cause of life-threatening infection in burn patients, premature babies, and other hospitalized patients. Although clinical trials on these other conjugate vaccines are not as advanced as trials of the Haemophilus influenzae vaccine, they are equally promising in that they all elicit high levels of protective antibodies in laboratory animals. Early trials of a conjugate vaccine for typhoid fever are also extremely promising.

Vaccine Development: Pertussis (whooping cough)

The current pertussis vaccine is reasonably effective but associated with a relatively high incidence of side effects including--albeit infrequently--seizures and other serious effects on the brain. The pertussis portion of DPT is made up of whole bacterial cells, and the noxious side effects may be due to components which are not necessary for immunization. NICHD scientists believe that one pertussis molecule, its toxin, is the sole protective antigen for this organism (i.e., the toxin is damaging but it also stimulates an immune response). These investigators have produced a vaccine made up of the toxoided (inactive) derivative of this antigen. Clinical evaluation of the first pharmaceutical lot of this toxoid vaccine in adults, and later in 18-month old children, has shown it to be safe and more immunogenic than the cellular pertussis vaccine currently in use. Clinical evaluation of the toxoid in younger infants injected either at 3, 5, and 7 months, or 3, 5, and 12 months, has also shown no local nor systemic adverse reactions, confirming the superior safety characteristics of this new vaccine. Expanded clinical trials will be necessary to be entirely certain of the vaccine's safety and efficacy.

Prevention Research Program

The NICHD's Prevention Research Program conducts investigations in the field of perinatal epidemiology which includes many of the key issues in maternal and child health such as perinatal and infant mortality and sudden infant death syndrome, intrauterine growth retardation or preterm delivery, congenital malformations, infant feeding practices and growth and development. The program is also involved at the present time in several clinical trials and community based interventions.

High Risk Pregnancy

The Institute is actively addressing questions of primary prevention in pregnancy, that is, finding ways to avoid bad outcomes such as miscarriages and birth defects. The Diabetes In Early Pregnancy Study has shown that insulin-dependent diabetic women who maintained good glucose control around the time they conceived were at no greater risk of having a miscarriage than non-diabetic women. Those diabetic women in poor glucose control were at considerably higher risk; their rate of pregnancy loss was as high as 35-40 percent (compared to 16 percent in the normal population). In addition, diabetic women who came for prenatal care prior to or immediately after conception have fewer malformed infants than those who do not receive medical attention very early in pregnancy (when the embryo's organs develop). Additional work remains to be done, however; the Diabetes In Early Pregnancy Study has also demonstrated that good glucose control alone is not sufficient to eliminate all excess malformations associated with diabetes. Other explanations for these malformations are being sought.

The Institute has examined the safety of new procedures being adopted by obstetricians. Chorionic villus sampling is a method of prenatal diagnosis in which cells are obtained early in the first trimester, thus providing an advantage over amniocentesis in terms of the time and speed of diagnosis. To evaluate the safety of chorionic villus sampling, the Institute led a collaborative study of 2,278 women who underwent chorionic villus sampling and 671 control women who underwent amniocentesis. The study found that accurate prenatal diagnosis was possible in 97.8 percent of the chorionic villus sampling procedures. The pregnancy loss rate was 0.8 percent higher in the chorionic villus sampling group than in the amniocentesis group, a statistically nonsignificant difference. There were no serious maternal infections in the chorionic villus sampling group. Thus, chorionic villus sampling was shown to be safe and effective.

The safety of in vitro fertilization (IVF) in terms of the outcomes of the children conceived by the procedure had not been systematically studied. The Institute and Eastern Virginia Medical School conducted a study of 83 IVF children and 93 matched control subjects. The IVF group did not have significantly more congenital malformations than the control group. Both groups did very well on tests of their mental and motor development (probably because of their high socio-economic status). The IVF group did slightly better than the control group, perhaps because of the "wantedness" of these children. This study demonstrated that children born after IVF are not at increased risk for birth defects or developmental delay.

Chloride Deficient Formula

Development was also the critical issue in a Congressionally mandated study of infants fed a chloride-deficient formula. The first part of a two part study on this issue is now complete. Using two school systems to locate children, investigators from NICHD identified 188 children exposed to these formulas and 466 children who received formula with adequate chloride. No differences on test scores were observed between the two groups. These data suggest that the chloride-deficient formula has not affected the long-term intellectual development of these children.

Prevention of Neural Tube Defects

Studies reporting that women who take multivitamin or folate supplements around the time that they conceive may be able to reduce their risk for having an infant with a neural tube defect (e.g. spina bifida) have generated much enthusiasm for taking vitamin supplements. However, there are serious questions about these studies because of the way in which subjects were recruited and because of possible bias in recalling vitamin use. NICHD undertook a collaborative study to look at the relationship between folate and other vitamin supplements taken around the time of conception and the risk for producing a child with a neural tube defect. Among 571 women who had a neural tube defect infant, 546 women who had a stillbirth or a conceptus with another malformation, and 573 who had a normal conceptus there was no difference in the use of either multivitamin or folate supplements around the time of conception. After adjusting for other risk factors, the likelihood of having a child with a neural tube defect was virtually identical whether a woman took vitamins or did not take vitamins around the time of conception. This study does not support the use of multivitamins or folate supplements to prevent neural tube defects.

Low Birth Weight Infants

Several studies are being conducted to better understand the etiology of low birth weight infants at high risk of mortality or morbidity. For example, a study of successive small-for-gestational age (SGA) births has been carried out in Alabama and Scandinavia. Women at high risk for delivering an SGA birth have been identified early in pregnancy and then studied longitudinally throughout the remainder of their pregnancy with anthropometric, dietary, clinical, psycho-social, and ultrasound measurements. The study infants have been followed-up through the first year of life for assessments of growth and achievement of developmental milestones. A follow-up developmental assessment of the study children through four years of age is expected to begin in FY 1990. In addition, a follow-back survey has recently begun in Missouri of all very low birth weight deliveries (<1500 g) with matched controls who are either moderately low birth weight (1500-2499 g) or normal birth weight ($\geq$2500 g). This study will assess both psycho-social and biomedical risk factors for the delivery of very low birth weight (and preterm) infants who are well known to have the highest risk of perinatal and infant mortality.

New Initiatives

In collaboration with the Baltimore City Health Department, we are developing an intensive outreach and case management program which is aimed at helping high risk pregnant women give birth to healthy infants. This is a multi-risk factor intervention which will, among other things, provide social support, outreach to enhance participation in prenatal care as well as compliance, and also specific interventions to address smoking, drug and alcohol abuse and to improve nutrition. The project will be geographically based in an area defined by census tracts which is characterized by a high rate of drug abuse among pregnant women, which is estimated to be approximately 30 percent. A good deal of this abuse, as in other inner city populations, is due to the use of crack cocaine. In view of the increasing evidence that crack cocaine is a risk factor for preterm delivery, an intervention to reduce crack cocaine abuse during pregnancy is a major component of this study. Support for this study is derived from private foundations and the City of Baltimore and donated staff time of a number of individuals from the city health department, the state health department and the University of Maryland. The Prevention Research Program is providing technical expertise to the design and development of this project and has assumed responsibility for the evaluation of the intervention. This project will make use of several innovative approaches to enhance the content of prenatal care by addressing behavioral risk factors in inner city populations, in line with the recommendations in the report of the Expert Panel on the Content of Prenatal Care, issued in October 1989.

There has been little, if any, change in the rate of preterm delivery in this country. In addition, we have observed during the last two years an increase in very low birth weight births (less than 3 1/2 lbs.) among Black Americans. Research leading up to the prevention of preterm delivery or of very low birth weight births, therefore, must receive a very high priority. Home monitoring as well as ambulatory monitoring of uterine contractions has been made possible through the development of compact devices weighing less than a pound which can be carried around the belt. It is hoped that through the use of these devices among women at high risk of preterm delivery, preterm labor can be easily predicted or earlier identified, thereby enhancing the efficacy of treatments to prevent or stop preterm labor. The current state of knowledge regarding the utility and efficacy of these devices is limited and based on several small scale clinical studies which were summarized at a recent workshop of the Prevention Research Program. While some studies showed promising results, it was uncertain whether these were the direct effect of the information derived from the devices and the therapy initiated or from the additional nursing support provided to the women using these devices. It would require a major and costly clinical trial to answer these questions. Such a trial could be important considering the continuing high rate of low birth weight in this country and the recent increase in very low birth weight births among Black Americans.

A small scale clinical trial conducted by the NICHD has demonstrated that calcium supplementation during pregnancy can reduce the risk of toxemia. A surprising finding of this trial was a significant reduction in preterm delivery among women receiving a supplementation. The NICHD is developing a large scale randomized clinical trial of calcium supplementation during pregnancy to confirm these provocative findings.

Birth defects remain an important cause of mortality and morbidity among infants. A consortium of centers is being organized to expedite the study of birth defects. In addition to follow up on the controversy of vitamin supplementation and the prevention of neural tube defects, the NICHD is planning studies which will measure directly multivitamin and folate levels in bloods obtained early in pregnancy in women who gave birth to children with neural tube defects.

National Institute of Child Health and Human Development

Research Management and Support

Authorization: Indefinite

Budget Authority:

1990 Appropriation		1991 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA
173	$21,776,000	176	$22,808,000	+3	+$1,032,000

Purpose and Method of Operation

This activity provides staff and resources for the administrative management and scientific direction of the Institute. Managerial and administrative services are provided through the following organizational components: The Office of the Director, the Office of Administrative Management (including financial management, personnel management, property control, and travel audit and control), the Office of Research Reporting, Office of Science Policy and Analysis, and the Office of Grants and Contracts.

The Scientific Review Program provides policy direction and coordination for all phases of scientific and technical merit review activities within NICHD involving research grants, research training grants, and research and development contracts. Additionally, this group serves in a liaison capacity for applicants, grantees, other components of NIH and the Department, advisory bodies, and interest organizations. The scientific program staffs of the Center for Research for Mothers and Children and the Center for Population Research concentrate their efforts on the scientific management of the Institute's grants and contracts and assist in the planning and development of new programs that will best accomplish the mission of the NICHD.

During 1991, this activity will continue to provide for the professional leadership and technical guidance needed to select the research questions which most merit investigation, to plan, direct, and implement all programs of the Institute, and to conduct a broad program of information dissemination to scientists and the public.

Rationale for the Budget Request

The 1991 request is $22,808,000, an increase of $1,032,000 above the 1990 level. This amount will cover built-in increases of $819,000 for centrally furnished services and pay-related costs. The program increase of $213,000 will provide for updated equipment needs and pay-related expenses for three additional FTEs.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Detail of Permanent Positions

	1989 Actual	1990 Appropriation	1991 Estimate
ES-4	11	14	14
Subtotal	11	14	14
GS/GM-15	26	26	26
GS/GM-14	46	47	47
GS/GM-13	32	32	32
GS-12	35	35	35
GS-11	30	30	30
GS-10	1	1	1
GS-9	23	23	23
GS-8	9	9	9
GS-7	30	34	34
GS-6	15	15	15
GS-5	18	22	22
GS-4	8	8	8
GS-3	3	3	3
Subtotal	276	285	285
Grades established by an act of July 1, 1944 (42 U.S.C., 270):			
Assistant Surgeon General	1	1	1
Director grade	22	22	22
Senior grade	3	3	3
Full grade	3	3	3
Senior assistant grade	1	1	1
Subtotal	30	30	30
Ungraded	6	6	6
Total permanent positions	323	335	335

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Advisory and Assistance Services

For FY 1991, the Advisory and Assistance Services budget will be $166,000, an increase of $12,000 over the FY 1990 amount, and will provide for additional costs for ad hoc scientific review functions as well as costs associated with the Institute's Advisory Council and Board of Scientific Counselors.

The majority of Consultant Services expenditures (either by purchase order or personnel appointments) are to accomplish scientific review functions which are mandated by the peer review process. Costs are to pay fees and expenses of scientific experts to review the grant and contract proposals received by the NICHD for which there is no other initial review provided by any other organization.

Internal controls are applied within the Institute to ensure appropriate use of consultant services. When such services involve review or advisory activities, purchase orders are submitted to the Institute Director for review and signature before approval of the purchase order by the Executive or Deputy Executive Officer of the Institute. The qualifications and appropriateness of both the consultant and the service are thus effected only by action of the Institute's senior management officials.

TUESDAY, MARCH 20, 1990.

OFFICE OF THE DIRECTOR AND BUILDINGS AND FACILITIES

WITNESSES

JOHN D. MAHONEY, ASSOCIATE DIRECTOR FOR ADMINISTRATION, NIH

DR. WILLIAM F. RAUB, ACTING DIRECTOR, NIH

NORMAN D. MANSFIELD, ASSOCIATE DIRECTOR FOR RESEARCH SERVICES, NIH

JOHN S. JARMAN, BUDGET OFFICER, OFFICE OF THE DIRECTOR, NIH

DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. NATCHER. We take up next the Office of the Director and Buildings and Facilities.

We have before the committee at this time Mr. Jack Mahoney, the Associate Director for Administration. With your permission, Mr. Mahoney, we will place your statement in the record in its entirety and go right to the questions.

Mr. MAHONEY. That would be fine, Mr. Chairman.

[The information follows:]

29-452 O—90—37

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Associate Director for Administration
Office of the Director

I am pleased to have the opportunity to discuss with the committee the FY 1991 budget requests for the Office of the Director and the Buildings and Facilities appropriations.

Office of the Director

The Office of the Director appropriation provides funds for offices that are primarily responsible for the development of NIH-wide policy and procedures as well as those that provide centralized administrative services in areas such as personnel and financial management.

This includes offices that coordinate trans-NIH initiatives, such as the recently established Offices of Minority Programs and Scientific Integrity. The Office of Minority Programs is being established to develop NIH-wide goals for minority research and training programs. The Office of Scientific Integrity was established to serve as a focal point within the PHS for implementing policies and procedures designed to safeguard the integrity of research conducted and supported by PHS agencies.

The request includes funding for an NIH Director's Discretionary Fund. This fund, which will be allocated to the individual components, will allow NIH to be more responsive to new issues, emergencies or research opportunities of high priority.

This appropriation also funds two major AIDS programs, the Office of AIDS Research and the Intramural AIDS Targeted Antiviral Program. The Office of AIDS Research oversees the development of AIDS-related policy and coordinates NIH intramural and extramural AIDS research. The Office is also responsible for the implementation and management of the NIH Loan Repayment Program, a program for repayment of a portion of the accumulated educational loan debt of health professionals who agree to conduct AIDS research as NIH employees. The Intramural AIDS Targeted Antiviral Program supports an NIH-wide initiative of basic research on the structure and function of the human immunodeficiency virus. Many of the best scientists at the NIH have been attracted by this program to work on AIDS for the first time.

Finally, this appropriation funds the Academic Research Enhancement Award (AREA) Program. This program provides important support to biomedical research programs at educational institutions that are not research-intensive.

The fiscal year 1991 request of $82,975,000 for the Office of the Director includes $35,791,000 for the support of the line and staff offices, $20,000,000 for the Director's Discretionary Fund, $13,747,000 for the AIDS Program, $2,065,000 for the Intramural Research in Diagnostic Radiology Program and $11,372,000 for the AREA Program.

Buildings and Facilities

The Buildings and Facilities appropriation provides funds for the design, construction, repair, and improvement of the clinical, laboratory, and supporting facilities of the NIH. The buildings and facilities program presently includes programs for campus infrastructure modernization and improvement, Clinical Center modernization, the renovation of the oldest laboratory buildings, animal facilities renovation and construction, AIDS-related construction and renovation, other ongoing construction projects, and repair and improvements.

The Infrastructure Modernization and Improvement Program is a critical element of this request. This Program identifies and provides for the replacement and expansion of the central plant equipment and the utility distribution systems, most of which have been in use since 1953. The primary goals are to correct safety deficiencies; restore and improve reliability and expand the capacity of the mechanical and electrical utility systems to meet current and future service demands; and improve efficiency of these systems to extend their useful life, conserve energy, and reduce costs. Preliminary cost estimates of the program are in excess of $150 million over a ten-year period. The request in FY 1991 provides for construction of a fifth boiler, enhancement of two chillers, increased piping capacity in the central plant, design for underground utility line replacement and expansion, and completion of PCB transformer replacement.

The Clinical Center Modernization Program began in 1979 as a multiyear program to address the issues of safety, hospital accreditation, modern procedures, equipment, and facilities for delivery of quality patient care and supporting research. An ongoing study has revealed considerable infrastructure deficiencies that could have a serious impact on the current and future Clinical Center research programs. Therefore, direction of the existing Clinical Center Modernization Program is being altered to provide more immediate attention to the most pressing safety issues, to maintain the hospital's accreditation, reduce costs, and to begin the process of correcting the infrastructure deficiencies. Corrections in all of these areas are critical to our ability to continue safe clinical research at NIH.

The renovation and modernization of our oldest laboratory buildings, intended to overcome shortcomings in safety and ability to support state-of-the-art research, is progressing. Buildings 8 and 4 are finished and Phase I construction of Building 5 will be complete this year. Rehabilitation for Buildings 2, 3, and 7 remain. Funds are requested this fiscal year for the completion of Building 5 construction and for Building 2 design as part of the long-term effort.

By constructing new and renovating existing animal facilities, the NIH is pursuing its goal of ensuring that all NIH animal facilities meet AAALAC standards. The initial phase, which included construction of two new buildings, major renovations of two buildings, and minor renovations of five buildings, will be completed in FY 1990. Funds requested in FY 1991 will provide continuing upgrade or construction of the central NIH animal facilities including Buildings 14 and 28 on the campus and facilities at the NIH Animal Center in Poolesville.

The FY 1991 request for AIDS facilities includes funds to complete the renovations at the Twinbrook II Building for NIAID AIDS research, the construction of a new primate facility for AIDS research, and the renovation or expansion of NCI AIDS laboratories. Other projects currently being designed or constructed are an addition to the Clinical Center and a new building at the Frederick Cancer Research Facility for NCI.

The FY 1991 request also includes funds for routine repairs and improvements to the main physical plant at Bethesda, Maryland, and field stations that are the responsibility of NIH. Individual projects supported with these funds are relatively small and of a recurring nature. The request will provide for the maintenance of our extensive physical plants and changes related to program needs.

Other ongoing construction projects include the Child Health and Neurosciences Facilities Program (Building 49 and related projects). This program will provide additional space for research laboratories, animal research and holding areas, and related administrative and support areas. Building 49 construction is entering Phase II, superstructure, with Phase III, the building envelope, major mechanical and electrical systems, and some interior finishes scheduled to begin later this year. Planning and design completion for the Consolidated Office Building or the Center for Biomedical Research Management is pending results of an ongoing environmental assessment. The National Institute of Environmental Health Sciences' research and facilities additions design is essentially complete. No funds have been requested for these projects in 1991.

The FY 1991 request of $88,600,000 for Buildings and Facilities provides $19,200,00 for the initial funding of infrastructure modernization and improvement at the NIH, $14,500,000 for the continuing renovation of the Clinical Center, $13,000,000 for the rehabilitation of the campus' oldest laboratory buildings, $18,500,000 for the renovation of animal facilities, $16,500,000 for the construction and renovation of laboratory space for AIDS research, and $6,900,000 for the continuing program of repairs and improvements. This is an increase of approximately $28 million over the FY 1990 level.

Thank you. I would be pleased to respond to any questions you may have.

JOHN DANIEL MAHONEY
Associate Director for Administration

Born February 19, 1945; Northampton, Massachusetts
Married, two children

Education. Baltimore Polytechnic Institute, Baltimore, MD, June 1962. B.A., University of Maryland, June 1966. M.B.A., University of Maryland, August 1968. New York University, January 1978-January 1979.

Professional History. 1968-1969, Management Intern, Naval Air Systems Command, Arlington, VA. 1969-1970, Systems Effectiveness Officer, Naval Air Systems Command, Arlington, VA. 1970-1972, Budget Analyst, National Institute of Mental Health, PHS, Rockville, MD. 1972-1975, Chief, Budget Management Branch, Alcohol, Drug Abuse and Mental Health Administration, PHS, Rockville, MD. 1974-1975, Acting Director, Division of Financial Management, Alcohol, Drug Abuse and Mental Health Administration, PHS, Rockville, MD. 1975-1979, Director, Division of Financial Management, Alcohol, Drug Abuse and Mental Health Administration, PHS, Rockville, MD. 1979-1984, Chief, Budget Branch, Office of the Assistant Secretary for Health, PHS, Rockville, MD. 1984-1986, Director, Office of Financial Management and Administrative Systems, Health Care Financing Administration, Baltimore, MD. 1986-Present, Associate Director for Administration, NIH, Bethesda, MD.

Honors, Awards. Special Achievement Award, 1974. PHS Special Recognition Award, 1976. Quality Increases, 1973 and 1979. PHS Superior Service Award, 1982. Secretary's Award for Exceptional Achievement, 1983.

Mr. NATCHER. Tell us who you have with you there at the table, please.

Mr. MAHONEY. Mr. Chairman, on the far left is Mr. Norman Mansfield, who is the Associate Director for Research Services at NIH; Mr. John Jarman, who is the Budget Officer for the Office of the Director, and of course, Dr. Raub and Mr. Williams.

DIRECTOR'S DISCRETIONARY FUND AND ONE PERCENT TRANSFER AUTHORITY

Mr. NATCHER. Thank you very much.

The President's budget, as you know, includes two proposals intended to give the Director an independent research budget. Would you explain to the committee now briefly how both the discretionary fund and the 1-percent transfer authority would work?

Mr. MAHONEY. Mr. Chairman, the discretionary fund represents a $20,000,000 request in the 1991 President's budget that would give the Director of the agency the flexibility to respond to high-priority research issues. The transfer authority would accomplish the same purpose in the sense that it would allow the transfer of up to a total of 1 percent of the total appropriations of NIH, although no more than 1 percent of any individual appropriation could be either taken or received.

The NIH Director currently has no general research resources directly under his/her control. The Institute of Medicine, in its review of NIH, recommended that a discretionary fund, available to the Director, would greatly enhance the flexibility of that position.

Mr. NATCHER. The 1 percent transfer authority could yield in excess of $80,000,000. Why would the Director need such a large amount?

Mr. MAHONEY. I think that in a practical sense, Mr. Chairman, when one looks at the language in the proposal, the amount of money that is taken from or received by any one appropriation is restricted to no more than 1 percent. The actual amount of funds that could ever be transferred in this manner would be far less than $80,000,000.

Mr. NATCHER. As you know, the transfer authority as currently proposed would not require Congressional approval. How could the committee be assured that this authority would not be used to overturn additions or reductions which might be approved by the Congress during the regular appropriations cycle?

CENTRAL SERVICE FUNDS

Mr. MAHONEY. I think common sense on our part, Mr. Chairman, would dictate that that not occur.

Mr. NATCHER. All right, I think that is a good answer.

Mr. Mahoney, would you explain to the committee briefly now which activities are financed under your two revolving funds, and tell us how these funds are financed?

Mr. MAHONEY. Mr. Chairman, we have two central funds, the Management Fund and the Service and Supply Fund. The programs that are financed by these activities are those of the Division of Research Services, which has recently been incorporated

into the National Center for Research Services, the Division of Computer Research and Technology, the Clinical Center, the Division of Research Grants, the Office of Research Services, and the Divisions of Procurement and Logistics.

The Management Fund provides for a number of centralized services to the Institutes for which we cannot construct rates because of the diverse nature of those activities and individual transactions. The Clinical Center is an example of that, where the Clinical Center provides the beds and the support for clinical research at NIH, but it is very difficult to construct an actual amount per service that is provided.

On the other hand, under the Service and Supply Fund, which is a revolving fund, we actually can construct a rate to charge the consumer for central services.

An example of that type of activity would be our Computer Center at NIH, where we can very easily construct an amount that we can charge an individual user for each computer job run at the Computer Center.

Mr. NATCHER. As you know, costs under the Management Fund increased by $70,000,000 in two years. Can you explain to the committee why costs under this fund increased by 13 percent in 1990 and are proposed to increase by another 7 percent in 1991?

Mr. MAHONEY. Mr. Chairman, for the Management Fund, the actual reason for the increase cuts across a wide spectrum of activities. I would be glad to submit for the record the complete list of those. Of note is the Clinical Center which is funded through the Management Fund and is responsible for a large share of the additional costs of the Management Fund. This was particularly true in 1990.

[The information follows:]

NATIONAL INSTITUTES OF HEALTH: MANAGEMENT FUND SUMMARY OF CHANGES—1989 ACTUAL THROUGH 1991 PRESIDENT'S BUDGET

[Dollars in thousands]

	Management fund	Percent change
1989 actual	$342,204	
Personal services—Annualization of January 1989 pay raise, within grades and fringe benefits	4,695	
Price level—inflation allowance	7,766	
Program change:		
CC—per legislation: Title XXXVIII salaries for nurses and allied health professionals	1,217	
New elevator maintenance contracts	1,243	
New rental office space—Executive Plaza	551	
1990 President's budget	357,676	
Personal services—January 1990 pay raise and fringe benefits	4,127	
Increase utilities and plant maintenance	4,554	
Program changes:		
CC—Per legislation: Doubling AIDS Outpatients [1]and title XXXVIII salaries for nurses and allied health professionals; Patient Care Unit renovations	15,377	
Hardware and software improvements for peer review system	698	
Engineering study of original hospital structure, increased plant maintenance contracts, increased hazardous waste surcharges and telecommunications improvements	3,294	
1990 column of 1991 President's budget	385,726	13
Personal services—Annualization of January 1990 pay raise plus January 1991 pay raise, within grades and fringe benefits	12,075	
Price level—inflation allowance	8,819	
Nuclear Magnetic Resonance program transfer from Service and Supply Fund	1,300	

NATIONAL INSTITUTES OF HEALTH: MANAGEMENT FUND SUMMARY OF CHANGES—1989 ACTUAL THROUGH 1991 PRESIDENT'S BUDGET—Continued

[Dollars in thousands]

	Management fund	Percent change
Program change:		
CC—Enhancement of Pediatric Medical Intensive Care Unit and increased maintenance of facilities	1,663	
Enhancements to scientific computing, parallel processing and peer review automation system	636	
Improvements to animal space for AAALAC accreditation	1,803	
Increased radioactive waste surcharges and meter mail equipment for new postal procedures	362	
1991 President's budget	412,384	7

[1] Funds were included in the Institutes' 1990 President's budget but were not included in the management fund (clinical center) at that time.

Mr. NATCHER. The latest 1990 estimate for the Management Fund is $28,000,000 higher than your original request last year. Can you tell us specifically why you are so far over budget in this account, and particularly in the areas of clinical services, peer review, and intramural research?

Mr. MAHONEY. The driving force in these additional costs is the cost of research at the Clinical Center. Of the total amount that you mentioned in your question, $28,000,000, over $15,000,000, is related to increased costs at the Clinical Center. Detailing those costs, about $7,000,000 is related to the Congressional requirement that we double the out-patient capacity of the Clinical Center for AIDS patients. While that is an increase in the Clinical Center's budget, it should not be interpreted as an additional tap on the Institutes, because funds were provided to the National Institute of Allergy and Infectious Diseases and to the National Cancer Institute for those activities.

There is about $6,000,000 that is related to a variety of other costs, primarily personnel costs. One of the mixed blessings that we have, Mr. Chairman, is that we have the ability now, with the passage of Title XXXVIII, to set the salary rates of nurses and other allied health care professionals at the going market rate. For this, we owe the Committee a great deal of gratitude.

Unfortunately, nursing costs in particular have risen dramatically. We are in a very competitive market, and so, in order to maintain that competitive edge, the additional cost is the result.

The final remaining element of that $15,000,000 increase is $2,000,000 for renovations of patient care units at the Clinical Center, primarily to make sure that we are in compliance with safety codes.

Mr. NATCHER. What level of confidence do you have in your 1991 request for the Management Fund?

Mr. MAHONEY. Mr. Chairman, the questions that you have asked are particularly appropriate, because there is great concern at the NIH over the growth of the Management Fund and also the increasing rate of the Clinical Center costs. We recently held a retreat of about 100 managers, including Dr. Raub, most of the Institute Directors, and the scientific directors, to discuss this.

It became clear from that retreat that there was a necessity by all parties to reanalyze the costs of the Clinical Center and to take the steps that are necessary to contain those costs. I think, in light

of the commitment that was made at that retreat and the agenda that has been put forward on cost containment, we have more confidence in the estimates this year than in the past.

Mr. NATCHER. As you know there is also an increase of $50,000,000 or 25 percent in the Service and Supply Fund between 1989 and 1991. Now, Mr. Mahoney, the committee was hoping that procurement reforms would reduce costs in this area.

Why 25 percent in two years, Mr. Mahoney?

Mr. MAHONEY. Mr. Chairman, there are a variety of activities that result in those increases. I think the most important point to make with regard to the Service and Supply Fund is that it is driven in part by our estimate of the demand that will exist for these services. The other element in the total cost is the rate that is charged for those services.

If the service components or the Institutes decide not to purchase services at the level that we have projected, the net result is that the costs to the Service and Supply Fund decline.

There have been a couple of activities that are worthy of note in the increase. One is $6,000,000 to consolidate the variety of maintenance contracts that we have throughout all of the Institutes. While this shows up as an increase in the Service and Supply Fund, what we have actually done is to take all of the individual contracts for the maintenance of scientific equipment that were awarded by the individual Institutes and consolidated them into the Service and Supply Fund. This actually is a cost-saving measure and should result in reductions in unit cost to the Institutes.

There is also a fair amount of increase in the Service and Supply Fund, both in 1990 and in 1991 related to equipment purchases that have to be made to gain AAALAC accreditation for our animal care facilities. Those should be one-time costs and, hopefully, accreditation will be achieved as a result of both these funds and those requested in the 1991 Buildings and Facilities budget for construction activities related to our animal facilities.

Mr. NATCHER. Mr. Mahoney, would it make sense to convert these revolving funds into separate appropriation accounts or limitations with amounts specified in them?

Mr. MAHONEY. We debated that, Mr. Chairman, at our retreat on the Clinical Center. I think the general consensus from most of us is that the flexibility that is allowed through the Service and Supply Fund and the Management Fund, and our ability to respond to individual issues leads us to conclude that this is probably the better way to go at this time.

Mr. NATCHER. Now, Mr. Mahoney, if you will, insert in the record at this point a table for fiscal years 1986 to 1990, showing the original budget requests for each fund, final expenditures and the percent increase over the previous year.

Also, if you will, include a table showing the portion of the 1991 budget for these funds which is expected to be derived from each NIH appropriation account.

Mr. MAHONEY. We would be glad to do that, Mr. Chairman.

[The information follows:]

National Institutes of Health
Management Fund and Service and Supply Fund
President's Budget and Actual Obligation Growth
1986 - 1990
(Dollars in Thousands)

	1986			1987			% Change		
	Pres. Budget	Col. of '87 PB	Actual Oblig.	Pres. Budget	Col. of '88 PB	Actual Oblig.	Pres. Budget	Col. of PB	Actual Oblig.
Management Fund	231,162	235,798	233,808	246,086	275,193	275,080	6.5%	16.7%	17.7%
Service & Supply Fund	165,151	181,252	167,223	188,870	195,186	187,265	14.4%	7.7%	12.0%
Total	396,313	417,050	401,031	434,956	470,379	462,345	9.8%	12.8%	15.3%

Note: The original 1987 Column of the 1988 President's Budget of $ 273,396,000 (Management Fund) was adjusted during the operating year for certain reimbursements including a one-time reimbursement from the Intramural Research Support Services activity for support of the AAALAC accreditation effort.

	1987			1988			% Change		
	Pres. Budget	Col. of '88 PB	Actual Oblig.	Pres. Budget	Col. of '89 PB	Actual Oblig.	Pres. Budget	Col. of PB	Actual Oblig.
Management Fund	246,086	275,193	275,080	295,719	298,893	305,212	20.2%	8.6%	11.0%
Service & Supply Fund	188,870	195,186	187,265	202,090	203,592	185,029	7.0%	4.3%	-1.2%
Total	434,956	470,379	462,345	497,809	502,485	490,241	14.4%	6.8%	6.0%

Note: The actual obligations in 1988 (Management Fund) reflected approved increases for the NIH AIDS research initiative; the expedited review of grant applications for AIDS research; the increased personnel costs for nursing care; increased rental costs and direct reimbursements during the operating year.

National Institutes of Health
Management Fund and Service and Supply Fund
President's Budget and Actual Obligation Growth
1986 - 1990
(Dollars in Thousands)

	1988			1989			% Change		
	Pres. Budget	Col. of '89 PB	Actual Oblig.	Pres. Budget	Col. of '90 PB	Actual Oblig.	Pres. Budget	Col. of PB	Actual Oblig.
Management Fund	295,719	298,893	305,212	310,019	331,122	342,204	4.8%	10.8%	12.1%
Service & Supply Fund	202,090	203,592	185,029	212,497	213,792	201,619	5.2%	5.0%	9.0%
Total	497,809	502,485	490,241	522,516	544,914	543,823	5.0%	8.4%	10.9%

Note: The actual obligations in 1989 (Management Fund) reflected approved increases for premium pay for nursing and allied health personnel, hospital improvements, corrective action required to maintain hospital accreditation by the JCAHO, plant maintenance and direct reimbursements during the operating year.

	1989			1990			% Change		
	Pres. Budget	Col. of '90 PB	Actual Oblig.	Pres. Budget	Col. of '91 PB	Est. Oblig.	Pres. Budget	Col. of PB	Est. Oblig.
Management Fund	310,019	331,122	342,204	357,676	385,726	385,726	15.4%	16.5%	12.7%
Service & Supply Fund	212,497	213,792	201,619	231,176	234,909	234,909	8.8%	9.9%	16.5%
Total	522,516	544,914	543,823	588,852	620,635	620,635	12.7%	13.9%	14.1%

National Institutes of Health
Management Fund and Service and Supply Fund
Distribution of FY 1991 Budget by Appropriation
(Dollars in Thousands)

NIH - ICDs	MF	SSF
NCI	$127,773	$50,141
NHLBI	51,502	13,659
NIDR	7,412	5,125
NIDDK	25,086	10,503
NINDS	25,357	8,508
NIAID	34,366	13,129
NIGMS	6,531	2,651
NICHD	24,230	10,200
NEI	9,253	3,888
NIEHS	2,461	3,105
NIA	6,799	3,358
NIAMS	8,111	1,742
NIDCD	1,206	252
NCRR	3,336	1,742
NCNR	604	379
FIC	893	606
NLM	8,712	3,585
OD	0	2,929
B&F	0	76
MF	0	40,219
SSF	7,959	0
Intrafund Billing - MF	23,115	0
- SSF	0	29,741
Subtotal NIH	$374,706	$205,538
Other DHHS Agencies	$37,678	$8,382
Outside DHHS Agencies	$0	$38,552
Total	$412,384	$252,472

NIH STAFFING LEVELS

Mr. NATCHER. As we discussed earlier, NIH has been given increased authority to set its own staffing levels. How do you plan to manage and control your staffing resources in the future, and tell us, if you will, who will set the staffing ceilings for each Institute?

Mr. MAHONEY. Mr. Chairman, as was stated in the overview session, we certainly are pleased with the outcome of the 1990 and 1991 budget discussions that resulted in greater flexibility regarding staffing ceilings.

We are currently asking each Institute for a detailed staffing plan and a rather detailed analysis of the number of FTEs that can be supported with the money that is allowed in the 1990 appropriation. We will be discussing the results of that analysis with Dr. Raub. The ultimate establishment of ceilings within the total allowed to NIH will be the prerogative of the NIH Director.

FUNDS AVAILABLE IN THE BUILDINGS AND FACILITIES APPROPRIATION

Mr. NATCHER. What is your current balance in the Building and Facilities accounts which, as you know, is no-year money?

Mr. MAHONEY. The total available that we expect in 1991 is approximately $13,000,000 in carry over authority.

NIH CONSTRUCTION PROGRAM

Mr. NATCHER. Are your construction programs generally on schedule or are they behind, Mr. Mahoney?

Mr. MAHONEY. That varies by individual project. Those are under the direction of Mr. Mansfield, the Associate Director for Research Services, who will respond to the question.

Mr. NATCHER. Go right ahead, Mr. Mansfield.

Mr. MANSFIELD. Mr. Chairman, we will submit a more complete answer for the record, but, in general, most of our large, complex projects run late. We have an aging facility with no turnaround space. That means construction is slowed while occupants are relocated from areas targeted for renovation. Often a series of relocations are necessary, each involving a renovation. Also, long lead times in the construction and procurement processes result in delays of these projects.

[The information follows:]

NATIONAL INSTITUTES OF HEALTH—CONSTRUCTION DELAYS

Many of our construction programs (projects) are completed on schedule, but most of our large and more complex projects do run late.

There are many factors that contribute to delays on large and complex research facilities construction projects. During the project design phase, delays occur in resolving design issues affecting installation of "state-of-the-art" and special purpose research equipment (e.g. cyclotrons, Magnetic Resource Imaging, Cat-Scan, ventilated animal racks, autoclaves, Special Refrigeration, etc.) There are also delays caused by late design adjustments to accommodate changes in technology and changes in program emphases and/or focus of specific research objectives. In addition delays can occur related to resolving site environmental and historic preservation issues with state and local government agencies.

During the construction phase, delays often occur due to availability and timeliness of delivery of "state-of-the-art" and special purpose research equipment, and fabrication and delivery of custom made building systems and equipment. The management and initiative of the general construction contractor and his coordination of subcontractors, or lack thereof, can be a significant factor in completing or not

completing a project on schedule. Unknown site conditions such as weather and foundation issues on new construction, and asbestos/chemical decontamination and utility relocation on renovation projects, can have significant impact on timely completion of projects. Another factor impacting timely project completion, especially renovation projects, is the lack of available "swing space" to house dislocated employees during construction; this often requires construction of additional multiple "swing spaces" (a musical chair scenario) to accomplish construction of a single project.

Finally, on large and complex projects of long duration, redesign and construction change orders delays almost always are required to adjust for changes in technology and focus of the research mission.

NIH ANIMAL FACILITIES

Mr. NATCHER. The 1990 and 1991 budgets include, as you know, almost $24,000,000 for improving NIH's animal facilities. How much has been spent on this project so far, and how much more will be needed?

Mr. MANSFIELD. Through 1989, we spent almost $22,000,000. We estimate that we will obligate another $6,000,000 in 1990, so by the end of this fiscal year, we will have spent approximately $28,000,000.

The 1991 budget has a request of $18,500,000, and another $25,000,000 will be required in the outyears to complete those projects.

Mr. NATCHER. We understand that NIH will be reviewed by AAALAC for accreditation of its animal facilities this fall. Is there any concern that NIH will not be accredited?

Mr. MANSFIELD. Based on our total plan and progress up until the time of the AAALAC review, we believe that AAALAC will provide accreditation of the entire facility, assuming funds are appropriated in FY 1991 and succeeding years.

Mr. NATCHER. If you will, insert in the record at this point a history table showing expenditures on animal facilities to date and planned for 1991 broken down by major project. If you would, we would appreciate it.

[The information follows:]

NATIONAL INSTITUTES OF HEALTH: BUILDINGS AND FACILITIES—AAALAC ACCREDITATION OF NIH ANIMAL FACILITIES

[Dollars in thousands]

Building	Obligated amounts			Total estimated costs
	1986–89 Actuals	1990 estimate	1991 estimates	
Initial Phase:				
6B	$5,836	$900	$	$6,736
7	626			626
10A	7,938	1,230		9,168
14D	2,208			2,208
14D Prime	182			182
29A	23			23
30	544			544
36	2,369			2,369
110A (NIHAC)	1,987	143		2,130
Miscellaneous	108			108
Subtotal	21,821	2,273		24,094

NATIONAL INSTITUTES OF HEALTH: BUILDINGS AND FACILITIES—AAALAC ACCREDITATION OF NIH ANIMAL FACILITIES—Continued

[Dollars in thousands]

Building	Obligated amounts			Total estimated costs
	1986–89 Actuals	1990 estimate	1991 estimates	
Phase to maintain accreditation				
Swine Facility, NIHAC		220	2,600	2,820
14C		950	5,600	6,550
14E		800	4,000	4,800
100 (NIHAC)		100	900	1,000
103/cagewash (NIHAC)		400		400
28 (ventilation/renovation)		620	2,000	2,620
T8 (NIHAC)		140	1,300	1,440
28A (necropsy)			700	700
Sewage Treatment (NIHAC)		240		240
Additional projects		100	1,400	1,500
Subtotal		3,570	18,500	22,070
Total	21,821	5,843	18,500	46,164

Note.—The estimates and ordering of projects for fiscal year 1990 and fiscal year 1991 may change as they proceed through the design process.

Mr. NATCHER. Dr. Raub, as you will recall, your first day here, and I believe with the Secretary, I talked with you a little bit about Jane Goodall coming to visit with me last year. She was very much concerned about this matter from the standpoint of humanely treating the animals.

You know, Dr. Raub, I receive letters from time to time from people; but very few people, Dr. Raub, ever say to me that animals should not be used. They just say treat them as humanely as possible, and that is the reason we are concerned about the facilities.

We know you are concerned about it, and that the Secretary is, and we would appreciate your attention. We know how you all feel about it. We have no problems.

Dr. RAUB. Yes, sir.

BUILDINGS AND FACILITIES FUNDING REQUIREMENTS

Mr. NATCHER. Last week, Dr. Raub testified briefly about the long-term needs for facility renovations which we understand may exceed $1,000,000,000 over the next decade. What are the major elements of this project, and when will you have a firmer idea of the total cost?

Mr. MANSFIELD. Within that total is $150,000,000 for what we call campus infrastructure that has been detailed in a plan we submitted to the committee at its request. This program involves the boilers, chillers, and transmission lines that move chilled water and steam around the campus and will take ten years to complete.

A second program is one that began in 1982, the renovation of a half-dozen laboratory buildings that are approximately 50 years old. The first two in the renovation plan have been completed, and we are working on the third. The remaining cost for that project is about $65,000,000.

The additional costs for animal facilities programs will be around $45,000,000. The projects have been identified and a detailed phasing is being worked out.

By far the biggest cost, which is not precisely known at this point, is for the modernization of the Clinical Center. The Clinical Center is almost 40 years old. Many of the utilities within that building have deteriorated and are not capable of supporting the existing operation. In order to remedy that, renovation must proceed on all support systems, so it is a long project, probably 15 to 20 years. We hope to have a detailed plan by the submission of the budget next year. The contractor that is doing the study for us estimates that improving and modernizing the Clinical Center infrastructure will cost between $400,000,000 and $800,000,000 depending on the option selected.

ACADEMIC RESEARCH ENHANCEMENT AWARDS PROGRAM

Mr. NATCHER. Last month, as you know, you held a conference for individuals interested in the research program for small colleges and universities, which you were good enough to invite me to attend.

As you know, I was not able to attend at that time. What can you tell me about the success of this program?

Mr. MAHONEY. Mr. Chairman, we felt it was a very successful conference. We were disappointed that you could not attend. However, your staff gave an excellent introduction to the conference. The purpose of the meeting was to provide the AREA grantees with a forum for feedback and to solicit suggestions on whether or not the program was successful or needed improvement.

There were about 450 attendees, which was a very large turnout. By and large, the feedback that we received was that the program was successful in training young and new scientists who had a limited research background.

A major recommendation that was made at the conference was that the AREA grant be renewable. Currently, the projects are funded for three years on a multi-year basis, and they are not renewable.

Mr. NATCHER. The committee understands that many more good applications have been approved than can be funded, as is the case throughout NIH. What is the general quality of these applications?

Mr. MAHONEY. The feeling, Mr. Chairman, is that the quality of the applications is good. The approval rates, as you mentioned, are in the 90-percent range, but the applications that are funded as a percentage of those approved in 1990 are estimated to be only about 17 percent.

Mr. NATCHER. Why was this program kept in the Office of the Director when the minority program was transferred to Research Resources?

Mr. MAHONEY. The answer to that, Mr. Chairman, relates to the administration of these programs. Funds for both of these programs were placed in the Office of the Director, but the National Center for Research Resources, formerly the Division of Research Resources, actually administered the RCMI program. That is different with respect to the AREA program which cuts across all of the

individual Institutes. There is a central review of AREA projects, and a central list that is prepared based on the quality of the applications. Since there is a much greater central review of the AREA program, it is logical for those funds to be budgeted in the OD.

OFFICE OF SCIENTIFIC INTEGRITY

Mr. NATCHER. Your 1991 request includes $1,400,000 for the new Office of Scientific Integrity. This is more than double the 1990 spending. How was this estimate derived?

Mr. MAHONEY. Primarily, Mr. Chairman, the amount of money that is budgeted for this is driven by the increased staffing needs for the Office of Scientific Integrity. We project in 1991 a staffing level of 15, which is an increase of nine over the 1990 budgeted level.

NIH CONSTRUCTION PROGRAM

Mr. NATCHER. The budget documents are a bit confusing with respect to the cost of the consolidated office building. Last week, I believe you said $133,000,000, the justifications, I believe, call for $119,000,000. Which is the correct figure, Mr. Mahoney?

Mr. MAHONEY. The confusion occurs from the fact that the costs of the Consolidated Office Building have grown past what was originally envisioned. The $133,000,000 cost is the amount of money that we currently project that the Consolidated Office Building will need. The $119,000,000, I believe, and Mr. Mansfield can correct me, was an earlier estimate.

Mr. MANSFIELD. The $119,000,000, Mr. Chairman, was in terms of 1990 dollars. The need to assess the environmental impact of the building is delaying its construction. The resulting delay and the effect of inflation in the intervening years result in the $133,000,000 estimate based on 1992 dollars.

Mr. NATCHER. The budget documents also describe a new building for AIDS research at the Frederick facility. Is this fully funded?

Mr. MANSFIELD. Yes, sir. This is for the National Cancer Institute research at Frederick. The originally planned building is fully funded. However, we are looking at the possibility of building a few extra floors on that building as opposed to constructing another facility.

EMPLOYEE RECRUITMENT

Mr. NATCHER. What is the current turnover rate for staff at NIH and how has this changed in recent years and particularly among top people?

Mr. MAHONEY. Mr. Chairman, the turnover rate at NIH on average is between 5 and 10 percent. For the top staff, the turnover rate is about 5 percent, particularly in our SES. While that turnover rate is low, that statistic masks the major problem that we face at NIH, that is, replacement. With respect to our senior scientists in the intramural program at the SES level, once there is a loss, it is very, very difficult to hire a replacement. The most impressive statistic in that respect, although we all wish we did not have this statistic, is that we have not been able to hire a senior intramural

research scientist in the SES from the outside in the past 11 years, and we have lost, in terms of the number of senior research scientists in the intramural program, 25 percent over that same period.

Mr. NATCHER. Several of the center directors and the new Director of the Deafness Institute have been recruited from outside NIH in the last few years, as you know. Can you tell us how many GS–15 or higher positions have been filled from outside NIH in recent years?

Mr. Mahoney, you might want to submit that for the record.

Mr. MAHONEY. Mr. Chairman, I will have to supply that for the record.

[The information follows:]

NATIONAL INSTITUTES OF HEALTH
Positions Filled From Outside NIH

During the last five fiscal years, NIH appointed 80 individuals to the Senior Executive Service (SES). Of these, 68, or 85 percent, were either promoted into the SES or selected from other SES positions within the Government. Only 12 individuals were appointed from outside the Government and none of these were appointed to positions involved in the direct conduct of clinical or basic biomedical research.

Over the same five fiscal years, 75 employees were appointed at grade GS-15 or GM-15 from outside NIH. Of those, 60 were scientists, appointed to all areas of intramural and extramural research, an average of twelve per year. The average number of scientists on board at that grade during that period was 368. Thus, only 3.3 percent of the average staff entered on duty from outside NIH.

Of the 60 scientists, 40, or an average of eight per year, were appointed to intramural positions. The average number of intramural scientists on board was 196. Thus, only 4.1 percent of the average intramural staff entered on duty from outside NIH.

Therefore, a total of 87 positions were filled at GS-15 or above from outside NIH over the past five fiscal years.

POSITIONS FILLED FROM OUTSIDE NIH
AT GS-15 AND ABOVE AND EQUIVALENT GRADES

Fiscal Years 1985 through 1989

Grade	FY 85	FY 86	FY 87	FY 88	FY 89	Totals	Ann. Avg. FY 85-89
GS/GM-15	17	9	11	17	21	75	15
GS/GM-16							
GS/GM-17							
GS/GM-18							
SES		1				1	0.2
SSS							
SES or SSS	1	4	3	4	5	17	3.4
210(g)							
CO-6	5	1	3	7	8	24	4.8
CO-7							
CO-8							
Totals	23	15	17	28	34	117	23.4

SCIENTIFIC POSITIONS FILLED FROM OUTSIDE NIH
AT GS-15 AND ABOVE AND EQUIVALENT GRADES

Fiscal Years 1985 through 1989

Grade	FY 85	FY 86	FY 87	FY 88	FY 89	Totals	Ann. Avg. FY 85-89
GS/GM-15	15	7	9	11	18	60	12
GS/GM-16							
GS/GM-17							
GS/GM-18							
SES							
SSS							
SES or SSS	1	3	3	3	4	14	2.8
210(g)							
CO-6	4	1	2	4	5	16	3.2
CO-7							
CO-8							
Totals	20	11	14	18	27	90	18

INTRAMURAL SCIENTIFIC POSITIONS FILLED FROM OUTSIDE NIH
AT GS-15 AND ABOVE AND EQUIVALENT GRADES

Fiscal Years 1985 through 1989

Grade	FY 85	FY 86	FY 87	FY 88	FY 89	Totals	Ann. Avg. FY 85-89
GS/GM-15	7	7	8	8	10	40	8
GS/GM-16							
GS/GM-17							
GS/GM-18							
SES							
SSS							
SES or SSS			1		1	2	0.4
210(g)							
CO-6	1			1		2	0.4
CO-7							
CO-8							
Totals	8	7	9	9	11	44	8.8

NON-INTRAMURAL SCIENTIFIC POSITIONS FILLED FROM OUTSIDE NIH
AT GS-15 AND ABOVE AND EQUIVALENT GRADES

Fiscal Years 1985 through 1989

Grade	FY 85	FY 86	FY 87	FY 88	FY 89	Totals	Ann. Avg. FY 85-89
GS/GM-15	8		1	3	8	20	4
GS/GM-16							
GS/GM-17							
GS/GM-18							
SES							
SSS							
SES or SSS	1	3	2	3	3	12	2.4
210(g)							
CO-6	3	1	2	3	5	14	2.8
CO-7							
CO-8							
Totals	12	4	5	9	16	46	9.2

SUPERCOMPUTER

Mr. NATCHER. Last year, Congress appropriated, as you know, $34,000,000 for a new supercomputer at NIH. Do you believe the final cost of this purchase will be above or below that level?

Mr. MAHONEY. Mr. Chairman, we are proceeding under the assumption that the final cost will be just under $34,000,000. We are proceeding with the procurement. Procurement of a computer of that size is a fairly long process in that it requires clearance from the General Services Administration. We are well on our way to gaining that clearance.

Mr. NATCHER. The committee understands that the deadline was last week for submitting notice of intent to apply to NIH for extramural facility grants. Can you tell us how many applications were received?

Mr. MAHONEY. Actually, Mr. Chairman, there are two RFAs that are out, one for the mouse production facility and the other for the extramural construction grants. The application receipt date for both of those RFAs is May 7, 1990. We asked the interested parties to submit a letter of intent by March 23, although that is not binding. Through telephone calls that we have received, we estimate that there will be in the neighborhood of about 100 applications for the extramural grant program.

There is an expectation of about three or so grant applications for the mouse breeding facility.

Mr. NATCHER. Is the $10,000,000 estimate for the animal facility flexible depending on the outcome of the peer review and NIH's view of of competing priorities?

Mr. MAHONEY. Dr. Raub may want to comment on this further, Mr. Chairman, but we have stated that the final amount of money awarded for the mouse production facility will be determined by the peer review process. If, as a result of that process, a recommendation is made for less than $10,000,000, then the award will be made for that amount.

Mr. NATCHER. Dr. Raub, would you care to comment on this.

Dr. RAUB. Mr. Chairman, I agree with that. The $10,000,000 is an indicator of the significance that the Department attaches to the mouse facility, particularly in the light of the specific authorization from the Congress for it. As Mr. Mahoney indicates, first and foremost, we will rely upon peer review assessment of the quality of the proposals and specifically on the budget assessment of the winning proposal. We would be hard-pressed to award more funds than is indicated by that review.

Whatever funds might be left over within the $10,000,000, we would propose to make available for the other RFA, where we expect very brisk competition.

CLOSING REMARKS ON NIH HEARINGS

Mr. NATCHER. Dr. Raub, this completes our hearings on the fiscal year 1991 budget for the National Institutes of Health. These hearings have covered more than 20 hours over an eight-day period. The hearings have been good. We want to thank you and your associates for their help as we review your request.

We hope to bring you a good bill, Dr. Raub, when we mark up later this spring, and we will look forward to your advice about spending needs throughout the Institutes. As we have proceeded with our hearings, Dr. Raub, as you will recall, I have said on a number of occasions the hearings have been good. We always look forward on this subcommittee to holding the hearings on the National Institutes of Health.

I want to thank all of you. The hearings have been excellent, and we appreciate it.

Dr. RAUB. Mr. Chairman, I know I speak for all of my colleagues in saying that we feel privileged for the amount of time and energy you and your colleagues have vested in us in this series of hearings. As always, you have been generous in your praise and constructive in your criticism, and you can be sure we will do our best to make you proud of the investment in the NIH.

Mr. NATCHER. Thank you very much.

The committee will now adjourn until 2:00 tomorrow afternoon.

[The following questions were submitted to be answered for the record:]

1990 MECHANISM TABLES

N-1. Mr. Natcher. The Committee would like to review the changes which have been made in your 1990 spending plans some of which reflect Congressional action and some of which are internal. Would you submit a set of 1990 mechanism tables for NIH as a whole showing your original request and the final spending plan.

Mr. Mahoney. [The information follows:]

National Institutes of Health

FY 1990 President's Budget and
FY 1990 Estimate
(dollars in thousands)

NIH TOTAL

Research Grants	FY 1990 President's Budget No.	FY 1990 President's Budget Amount	FY 1990 Estimate No.	FY 1990 Estimate Amount
Research Proj.:				
Noncompeting	15692	$3,313,752	15683	3,231,848
Admin. supp.	(462)	18,983	(469)	22,764
Competing...	4719	1,002,738	4,633	943,345
Subtot.,RPG.	20411	4,335,473	20316	4,197,957
Research Ctrs:				
Spec/comp...	404	407,179	418	417,810
GCRC.....	78	115,668	78	115,284
Biotech.....	62	32,133	59	32,074
LASPR.....	51	49,892	53	50,433
RCMI.....	0	17,503	17	19,337
Subtotal..	595	622,375	625	634,938
Other Res.:				
Careers	1561	108,375	1539	104,856
Clin. ed....	35	2,082	29	2,942
Coop. cl....	233	71,778	248	77,324
BRS.....	137	34,303	790	78,788
MBRS.....	98	38,985	98	39,622
Other.....	1067	72,271	1185	75,206
Subtotal..	3131	327,794	3889	378,738
Total,RGs...	24137	5,285,642	24830	5,211,633
Training				
Indiv.....	1728	45,559	1944	50,542
Instit.....	8756	213,913	9851	236,120
Total, Trng.	10484	259,472	11795	286,662
R&D Contracts.	1514	577,446	1345	576,495
Intramural ...		849,422		855,947
RM&S		300,964		317,713
Control.....		74,100		74,944
Construction..		0		16,272
Total, IRDs...		7,347,046		7,339,666
Nat'l. Library of Medicine		82,596		85,728
Office of the Director		78,155		89,916
Buildings and Facilities		21,600		61,042
TOTAL, NIH		7,529,397		7,576,352

PHYSICIANS COMPARABILITY ALLOWANCE

C-1. Mr. Conte. The maximum PCA allowance is $20,000. Is that correct? For how long has that been the maximum?

Mr. Mahoney. The PCA was last reauthorized in 1987, at which time the maximum bonus levels were doubled (from $7,000 to $14,000 for physicians with two years or less Federal service and from $10,000 to $20,000 for physicians with over two years service) at the request of the Administration.

The maximum PCA allowance is $20,000 per year for a physician entering into a contract for a two-year service obligation. The maximum PCA allowance for a one-year service obligation is $16,000. The following variables determine the exact amount of PCA payments: grade level, board certification, length of service obligation (one or two years), and complexity of assignment.

The President signed Public Law 100-140 on October 26, 1987, authorizing the extension of PCA through September 30, 1990, and raising the maximum allowance to $20,000.

C-2. Mr. Conte. In your professional judgment, what should be the level of the PCA, if it is renewed?

Mr. Mahoney. Each agency should establish criteria for the amount of PCA paid to each physician. These criteria should include the scarcity of medical specialty required for the position, board certification requirements of the position, and administrative and managerial responsibilities.

C-3. Mr. Conte. How many physicians at NIH currently receive the PCA?

Mr. Mahoney. Currently, 291 NIH physicians receive PCA.

C-4. Mr. Conte. Do all receive the maximum?

Mr. Mahoney. No. Only 108 NIH physicians receive the maximum PCA amount of $20,000 per year.

C-5. Mr. Conte. Is there any pending legislation that would renew the PCA?

Mr. Mahoney. To the best of our knowledge there is no legislation currently pending that would renew the PCA program.

DIAGNOSTIC RADIOLOGY

C-6. Mr. Conte. Last year this committee heard testimony on the need for a major intramural research program in diagnostic radiology at NIH. The intention was to develop a research laboratory in radiology--one that would carry out NIH's own program of basic and applied research, enhance the research capabilities of other intramural research teams, assist the extramural imaging research capabilities of other intramural research teams, assist the extramural imaging research programs, and provide a center for training. The Conjoint

Committee on Diagnostic Radiology endorsed the establishment of an imaging laboratory on the NIH campus. This endorsement for a laboratory was the basis for both the House and the Senate to include language on the need for this center. We provided $2 million for this specific activity.

It is my understanding that NIH's plan is to develop just a radiology post-doctoral training program at this time, not a laboratory.

A fellowship program, down the road, would maximize its fullest potential if there is a central, cohesive laboratory program.

Do you plan to develop an intramural laboratory in radiology, as intended by the Congress?

Mr. Mahoney. The Committee report language and the Appropriation state that the Director of NIH is encouraged to "establish an intramural research program for diagnostic radiology." NIH is in the process of fulfilling that charge.

Following passage of the FY 1990 Appropriation, the Director of NIH appointed a radiology research planning group, chaired by the Deputy Director for Intramural Research. As part of the planning process, the Acting Director of NIH and the Deputy Director for Intramural Research met with members of the Conjoint Committee. Recommendations from the Conjoint Committee, the advice of other leading academic radiologists, and the professional judgment of the intramural NIH scientists expert in imaging research have formed the basis of the NIH plan for building an intramural radiology research program. Although the advice of the Conjoint Committee has been important in the planning process, the Director of NIH is responsible for determining how best to construct an intramural research program.

Members of the Conjoint Committee appear to be concerned that the NIH radiology research program will not begin with the development of a central imaging laboratory that will serve as the training location for Radiology Research Fellows. Our judgment is that beginning with the development of a single research laboratory would be a classic instance of putting the cart before the horse. Instead, we intend to develop a program incrementally, capitalizing upon the important strengths in imaging technology already found in the intramural program. The program will have several components including training research fellows and the development of laboratory-based research programs.

With respect to research training, we expect to work cooperatively with the Conjoint Committee to recruit three to five radiologists annually to NIH for a two-year, post doctoral research training program. The Research Fellows will very likely come from extremely diverse backgrounds, holding graduate degrees in fields such as computer science, physics and engineering, as well as medical degrees and specialty training in radiology. The Fellows will accordingly have research interests too diverse to be satisfied in a central radiology laboratory. Some will wish to work with monoclonal antibody development, others in computer science and imaging techniques and still others in more classic fields of radiological research. Magnetic resonance imaging is expected to be the modality of greatest interest to the Research Fellows. Accordingly, funds available in the FY 1990 Appropriation are being utilized to

purchase a research NMR device to be managed by the Director of the Radiology Research Program.

In addition to the NMR device, we anticipate purchasing state-of-the-art, multi-modality computer imaging stations that will permit the Fellows to do comparative research involving NMR, CAT and other diagnostic imaging systems.

Recruitment of a program director is underway. It is our expectation that the program director will develop his or her own research laboratory, in the normal pattern of intramural research. It is likely that one or more of the Research Fellows will elect to work in the Director's laboratory and that it will, over time, evolve into a significant research program.

CONTE BUILDING (BUILDING 49)

C-7. Mr. Conte. As you know, I have maintained a special interest in the planning and construction of the new child neuroscience research building. The building will be a central focus for child neurologic studies and will house the best scientists in the field. What is the status of the actual construction of the building?

Mr. Mansfield. Final design of the Child Health and Neurosciences Building (49) began in November 1988. Construction of the foundation and site utilities began in July 1989 and was completed in January 1990. The contract for the building superstructure was awarded in January 1990, and we plan to begin construction of the building shell and major mechanical and electrical systems in July 1990.

C-8. Mr. Conte. How much is needed to continue the project in FY 1991?

Mr. Mansfield. The President's Budget includes no funding for the building in FY 1991. However, if funding is provided in FY 1991, $35.0 million would be required to complete the entire Child Health and Neurosciences Facilities program. The program includes the construction of Building 49, expansion of Building 6B, a small tower addition to Building 30, infrastructure support facilities, and a multi-level parking structure. However, if funding is not provided until FY 1992, $38.5 million would be required to complete the program.

C-9. Mr. Conte. Why didn't the request provide funds for the building?

Mr. Mansfield. The NIH has a number of buildings in serious need of repair and the infrastructure supporting all of its buildings are short of capacity and increasingly subject to failure. Some of our laboratories and patient care units do not provide adequate safety, and many animal facilities need to be upgraded to meet the standards necessary for proper care and use of animals. In addition, renovation and construction is necessary to ensure safe, effective facilities for AIDS research.

While funds for the entire Child Health and Neurosciences Facilities program could be used in FY 1991, funding is more urgently needed for the current projects identified in our FY 1991 Buildings and Facilities request.

C-10. Mr. Conte. The establishment of the Senior Biomedical Research Service will help address the salary and retirement system problems that have made it difficult for NIH to recruit and retain personnel. Is the availability of quality child care an important consideration to the support and professional staff at NIH?

Mr. Mansfield. The availability of child care is an important factor in the NIH's ability to recruit and retain support and professional staff. The NIH has long recognized that in order to attract qualified professional and support staff, it must provide a first class working environment that includes quality and affordable child care. This is particularly important since salaries are not competitive for many of these jobs. In an effort to move to the forefront of this area, an NIH Day Care Committee has been established to assess the current and future day care needs of NIH employees.

C-11. Mr. Conte. Tell us about the availability of child care services at NIH.

Mr. Mansfield. There are currently three NIH-sponsored day care centers: two on the NIH campus in Bethesda (one preschool and one infant care center) and one on the NIEHS North campus in North Carolina. There is also one non-government sponsored child care center in Bethesda that services approximately 140 children of NIH employees. We are investigating the feasibility of expanding the campus program and adding child care centers for our off-campus (leased) facilities at the Westwood and Executive Plaza Buildings, as well as at the Frederick Cancer Research Facility.

C-12. Mr. Conte. Are they adequate to serve both the current and future demand for services?

Mr. Mansfield. No. Currently, there is a two-year wait for the preschool program on campus. Although the wait for the infant care is not as long, the center is housed in a temporary building that allows for no program expansion and has inadequate outdoor play area. As indicated in response to your previous question, there are no NIH sponsored day care centers to service thousands of off-campus NIH employees.

C-13. Mr. Conte. Are the costs reasonable?

Mr. Mansfield. Although the fees charged for day care are competitive and most of the day care providers incorporate a sliding fee scale, the costs are not affordable for many low and moderate income employees.

C-14. Mr. Conte. Can NIH expand and subsidize the cost of child care services without additional legislation?

Mr. Mansfield. We can expand child care services without additional legislation, but can do little to make it affordable to our low and moderate income employees without legislative authority.

SENIOR BIOMEDICAL RESEARCH SERVICE

C-15. Mr. Conte. For the record, please estimate the cost of implementing the Senior Biomedical Research Service at NIH and ADAMHA, based on the provisions of my bill.

Mr. Mahoney. We project that the initial implementation of the provisions of your bill for NIH and ADAMHA would cost approximately $10.1 million more than our current personnel expenditures for scientists.

DISCRETIONARY FUND

C-16. Mr. Conte. This budget provides for $20 million for a NIH director's discretionary fund. We put money in the bill last year but by the time it came out of committee, it disappeared. If this fund was available last year, in what areas could you have used the fund?

Mr. Mahoney. Had the fund been available for FY 1990, NIH could use it to narrow the range of downward negotiations and award rates for research project grants across the Institutes. The fund could also be used to support a few additional clinical trials.

C-17. Mr. Conte. This budget makes a big push for the upgrading of the infrastructure at NIH. Even Secretary Sullivan called it a major priority in the whole HHS budget. Shouldn't there be a long-term plan to anticipate the wear and tear of these buildings?

Mr. Mansfield. Although the NIH has had an ongoing program for facility maintenance, repair, and improvements, we are in the process of developing a more comprehensive program that will establish short and long-range strategies for scheduled repair and replacement of our facilities and supporting utilities. There are a number of components to our plan: (1) the NIH program for general maintenance, repair, and improvement is being reevaluated to develop comprehensive surveys of our facilities that will identify a program of priority repairs and replacements, scheduled over a five-year period and updated annually; (2) many of the major campus utility systems deficiencies are planned for correction under the NIH Infrastructure Modernization and Improvement Program (IMIP). A ten-year, $150 million plan has been submitted to the Committee at its request; (3) we are in the process of developing a comprehensive renovation/alteration plan for the Clinical Center to correct safety deficiencies and obsolete, undersized, and inadequate utility systems. This program will take 10 to 20 years to complete and preliminary cost estimates from a contractor study currently underway range from $400 to $800 million. We expect to complete our plan in time for discussion at the FY 1992 hearings; (4) In 1982, we began work on a careful plan to modernize six laboratory buildings, now approximately 50 years old and suffering from safety

deficiencies and obsolescence. We have completed two of these buildings, are half-way through the third, and hope to finish the remaining three in seven to ten years. We expect this building renovation/replacement programs to continue as other laboratory buildings are evaluated, as described above in (1); and finally, (5) we have a detailed plan for modernizing our animal facilities to achieve and maintain AAALAC accreditation for the NIH campus. That program, begun in 1986, will have spent $27.7 million through the end of FY 1990. To carry out the plan we will need the $18.5 million requested in FY 1991 and $25.2 million subsequently.

NIH CAMPUS CAPACITY

C-18. Mr. Conte. What is the maximum number of major buildings that the campus can support?

Mr. Mansfield. NIH has six major buildable sites available on the Bethesda campus for future expansion. This figure does not include the site selected for the construction of the planned Consolidated Office Building (COB). In addition, there are five smaller sites adjacent to existing buildings that could support some expansion to the existing structures. These major and minor buildable sites are available only from the land availability perspective. The NIH infrastructure is not currently capable of providing complete utility services to new construction efforts that are not already programmed. A ten-year effort has recently been initiated to repair, replace and expand the utility generating and distribution systems to provide for current, as well as future utility requirements. In addition, the NIH is in the process of revising its 1972 Master Plan, and reevaluating the original premises of the plan. It is envisioned that maintaining the campus-like atmosphere and the buffer zone concept around the campus perimeter will be of high priority and revalidated. The amount of additional growth the campus can support, including the maximum number of buildings that can be built, will be determined by these premises, which will address not only infrastructure and service capabilities, but also environmental concerns, such as the amount of traffic that will be generated on the internal and surrounding road networks and air quality. Integration of all support and environmental issues needs to be accomplished prior to utilizing any of the available building sites.

C-19. Mr. Conte. How many buildings are there now?

Mr. Mansfield. There are 77 buildings on the Bethesda campus. This number includes the following general use categories: laboratories, offices and administration, computer research labs, animal labs and holding, housing, general service, storage, electrical power vaults, central utility, research hospital, fitness, training center, service garages, infant care, and multi-level parking garages.

In addition to the 77, there is one new building currently under construction, Building 49, and two being planned: the COB and the FDA addition to Building 29, 29B.

20. Mr. Conte. What is the parking situation?

Mr. Mansfield. There are about 7,700 employee parking spaces available for a work force of approximately 14,000. Visitor, consultant, and patient parking approaches 1,000 spaces for 3,000 to 4,000 daily visitors. Employee parking spaces are available on a first-come, first-served basis through a permit system that includes preferential parking for car pools and van pools.

The NIH Bethesda campus faces two major transportation problems: traffic congestion and parking. The campus is located in a metropolitan area that has experienced tremendous growth and the road system is inadequate for the existing traffic load. This has resulted in traffic congestion and gridlock on the road network surrounding NIH, particularly during the morning and evening commuting periods. Parking on the Bethesda campus is also a serious problem due primarily to growth in the campus population that has not been accompanied with additional parking capacity. The situation will be further impaired with the completion of the Child Health and Neurosciences Building 49 unless we are able to construct its associated multi-level parking structure. Finally, the construction of the Consolidated Office Building will exacerbate the situation by bringing an additional 3,000 employees to the campus every day.

C-21. Mr. Conte. How will you address the parking problem?

Mr. Mansfield. We are addressing the parking problem in the context of developing an NIH Transportation Management Plan (TMP). This plan will build upon a comprehensive assessment of our parking and transportation problems and the unusual requirements of the research center on the NIH campus. It will outline short and long-term strategies for improvements and mitigative measures. The plan, in the final stages of NIH review, will be forwarded for review and approval by the PHS, National Capital Planning Commission, Maryland National Capital Park and Planning Commission, and the Montgomery County Departments of Planning and Transportation, before implementation.

NIH is also participating in several local transportation organizations aimed at improving the local transportation problems of employers and residents. Among these organizations are the Transportation Action Partnership (TAP), Keep Montgomery County Moving (KMCM), and the Bethesda Ridesharing Office.

NIH RESIDENCES

C-22. Mr. Conte. I understand a number of buildings are used as residences for a number of people associated with NIH. How many people reside on the campus?

Mr. Mansfield. A total of 130 people reside on the NIH campus--102 in the apartment house and 28 in the quarters.

C-23. Mr. Conte. Do you anticipate a greater demand for residences on campus?

Mr. Mansfield. No, I do not anticipate a greater demand for residence on campus at this time. There are currently no waiting lists for occupancy.

MINORITIES EMPLOYED BY NIH

Mr. Stokes: Please provide a list showing the number and percentage of minorities employed by NIH at each grade level, broken down by Institute.

Mr. Mahoney: The information follows:-

04-11-90
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(NUMBER & PERCENTAGES) NIH EMPLOYEES AS OF SEPTEMBER 1989, BY ICD, PP, AND GRADE
ICD: NCI

PP	GRADE	TOTAL EMPLOYMENT	NO. OF MINORITIES	PERCENT OF TOTAL
CC	03	5	0	0.0
	04	12	0	0.0
	05	46	4	8.6
	06	81	5	6.1
	07	1	0	0.0
	08	1	0	0.0
	TOTAL PP	146	9	6.1
ES	03	4	1	25.0
	04	16	0	0.0
	05	1	0	0.0
	TOTAL PP	21	1	4.7
GM	13	69	7	10.1
	14	116	13	11.2
	15	115	12	10.4
	TOTAL PP	300	32	10.6
GS	01	2	0	0.0
	02	2	0	0.0
	03	8	6	75.0
	04	35	17	48.5
	05	76	43	56.5
	06	139	39	28.0
	07	215	53	24.6
	08	51	6	11.7
	09	179	47	26.2
	10	1	0	0.0
	11	231	38	16.4
	12	192	30	15.6
	13	78	9	11.5
	14	72	11	15.2
	15	9	0	0.0
	TOTAL PP	1,290	299	23.1
	TOTAL ICD	1,757	341	19.4

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(NUMBER & PERCENTAGES) NIH EMPLOYEES AS OF SEPTEMBER 1989, BY ICD, PP, AND GRADE
ICD: NHLBI

PP	GRADE	TOTAL EMPLOYMENT	NO. OF MINORITIES	PERCENT OF TOTAL
CC	03	1	0	0.0
	04	4	1	25.0
	05	13	1	7.6
	06	34	2	5.8
	07	1	0	0.0
	TOTAL PP	53	4	7.5
ES	02	1	0	0.0
	03	2	0	0.0
	04	14	1	7.1
	05	3	0	0.0
	06	1	0	0.0
	TOTAL PP	21	1	4.7
GM	13	22	2	9.0
	14	46	9	19.5
	15	42	3	7.1
	TOTAL PP	110	14	12.7
GS	02	4	2	50.0
	03	3	0	0.0
	04	18	9	50.0
	05	20	12	60.0
	06	55	21	38.1
	07	117	34	29.0
	08	27	8	29.6
	09	55	14	25.4
	10	8	3	37.5
	11	68	18	26.4
	12	46	9	19.5
	13	36	3	8.3
	14	30	4	13.3
	15	2	1	50.0
	TOTAL PP	489	138	28.2
	TOTAL ICD	673	157	23.3

04-11-90
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(NUMBER & PERCENTAGES) NIH EMPLOYEES AS OF SEPTEMBER 1989, BY ICD, PP, AND GRADE
ICD: NIDR

PP	GRADE	TOTAL EMPLOYMENT	NO. OF MINORITIES	PERCENT OF TOTAL
CC	03	1	1	100.0
	04	1	0	0.0
	05	4	1	25.0
	06	15	0	0.0
	07	1	0	0.0
	TOTAL PP	22	2	9.0
ES	03	1	0	0.0
	04	4	0	0.0
	TOTAL PP	5	0	0.0
GM	13	11	1	9.0
	14	14	1	7.1
	15	20	0	0.0
	TOTAL PP	45	2	4.4
GS	03	3	1	33.3
	04	3	2	66.6
	05	13	6	46.1
	06	16	4	25.0
	07	31	11	35.4
	08	11	2	18.1
	09	24	7	29.1
	10	1	0	0.0
	11	24	4	16.6
	12	23	1	4.3
	13	6	1	16.6
	14	11	4	36.3
	TOTAL PP	166	43	25.9
	TOTAL ICD	238	47	19.7

(NUMBER & PERCENTAGES) NIH EMPLOYEES AS OF SEPTEMBER 1989, BY ICD, PP, AND GRADE
ICD: NIDDK

PP	GRADE	TOTAL EMPLOYMENT	NO. OF MINORITIES	PERCENT OF TOTAL
CC	03	1	1	100.0
	04	1	1	100.0
	05	3	0	0.0
	06	24	3	12.5
	07	2	0	0.0
	TOTAL PP	31	5	16.1
ES	02	1	0	0.0
	03	1	0	0.0
	04	16	0	0.0
	TOTAL PP	18	0	0.0
GM	13	9	1	11.1
	14	15	0	0.0
	15	37	4	10.8
	TOTAL PP	61	5	8.1
GS	03	2	1	50.0
	04	9	5	55.5
	05	16	8	50.0
	06	30	7	23.3
	07	55	16	29.0
	08	22	4	18.1
	09	29	11	37.9
	10	1	0	0.0
	11	31	6	19.3
	12	40	8	20.0
	13	24	7	29.1
	14	30	3	10.0
	15	13	1	7.6
	TOTAL PP	302	77	25.4
	TOTAL ICD	412	87	21.1

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PRODUCED BY SAB/DPM - TAPS 2805 (A)

(NUMBER & PERCENTAGES) NIH EMPLOYEES AS OF SEPTEMBER 1989, BY ICD, PP, AND GRADE
ICD: NINDS

PP	GRADE	TOTAL EMPLOYMENT	NO. OF MINORITIES	PERCENT OF TOTAL
CC	03	1	0	0.0
	04	2	0	0.0
	05	6	0	0.0
	06	19	1	5.2
	08	1	0	0.0
	TOTAL PP	29	1	3.4
ES	03	1	0	0.0
	04	13	0	0.0
	05	1	0	0.0
	TOTAL PP	15	0	0.0
GM	13	16	2	12.5
	14	22	2	9.0
	15	22	1	4.5
	TOTAL PP	60	5	8.3
GS	02	2	1	50.0
	03	5	1	20.0
	04	10	4	40.0
	05	33	12	36.3
	06	44	20	45.4
	07	61	17	27.8
	08	14	0	0.0
	09	58	24	41.3
	10	2	0	0.0
	11	58	8	13.7
	12	27	3	11.1
	13	20	2	10.0
	14	19	2	10.5
	15	3	1	33.3
	TOTAL PP	356	95	26.6
	TOTAL ICD	460	101	21.9

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(NUMBER & PERCENTAGES)

NIH EMPLOYEES AS OF SEPTEMBER 1989, BY ICD, PP, AND GRADE
ICD: NIAID

PP	GRADE	TOTAL EMPLOYMENT	NO. OF MINORITIES	PERCENT OF TOTAL
CC	03	1	0	0.0
	04	1	0	0.0
	05	14	0	0.0
	06	37	0	0.0
	08	1	0	0.0
	TOTAL PP	54	0	0.0
ES	01	1	0	0.0
	02	3	0	0.0
	03	1	0	0.0
	04	7	1	14.2
	TOTAL PP	12	1	8.3
GM	13	19	5	26.3
	14	39	4	10.2
	15	37	6	16.2
	TOTAL PP	95	15	15.7
GS	04	10	2	20.0
	05	46	18	39.1
	06	40	13	32.5
	07	84	21	25.0
	08	16	2	12.5
	09	77	15	19.4
	10	1	0	0.0
	11	98	25	25.5
	12	67	13	19.4
	13	24	4	16.6
	14	24	4	16.6
	15	3	0	0.0
	16	1	0	0.0
	TOTAL PP	491	117	23.8
	TOTAL ICD	652	133	20.3

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PRODUCED BY SAB/DPM - TAPS 2805 (A)

(NUMBER & PERCENTAGES)

NIH EMPLOYEES AS OF SEPTEMBER 1989, BY ICD, PP, AND GRADE
ICD: NIGMS

PP	GRADE	TOTAL EMPLOYMENT	NO. OF MINORITIES	PERCENT OF TOTAL
CC	06	1	0	0.0
	TOTAL PP	1	0	0.0
ES	01	2	0	0.0
	03	1	0	0.0
	04	2	0	0.0
	05	1	0	0.0
	TOTAL PP	6	0	0.0
GM	13	8	1	12.5
	14	20	5	25.0
	15	11	2	18.1
	TOTAL PP	39	8	20.5
GS	02	1	1	100.0
	03	2	0	0.0
	04	13	9	69.2
	05	15	4	26.6
	06	12	3	25.0
	07	20	5	25.0
	08	9	3	33.3
	09	5	2	40.0
	10	1	0	0.0
	11	3	2	66.6
	12	16	3	18.7
	13	1	1	100.0
	TOTAL PP	98	33	33.6
	TOTAL ICD	144	41	28.4

04-11-90
PRODUCED BY SAB/DPM - TAPS 2805 (A)

(NUMBER & PERCENTAGES)

NIH EMPLOYEES AS OF SEPTEMBER 1989, BY ICD, PP, AND GRADE
ICD: NICHHD

PP	GRADE	TOTAL EMPLOYMENT	NO. OF MINORITIES	PERCENT OF TOTAL
CC	03	1	0	0.0
	04	3	1	33.3
	05	5	1	20.0
	06	19	3	15.7
	07	1	0	0.0
	TOTAL PP	29	5	17.2
ES	04	10	0	0.0
	TOTAL PP	10	0	0.0
GM	13	15	4	26.6
	14	25	4	16.0
	15	23	4	17.3
	TOTAL PP	63	12	19.0
GS	03	5	2	40.0
	04	12	6	50.0
	05	16	4	25.0
	06	14	9	64.2
	07	52	11	21.1
	08	14	1	7.1
	09	18	5	27.7
	10	2	1	50.0
	11	30	9	30.0
	12	31	6	19.3
	13	16	3	18.7
	14	20	2	10.0
	15	2	0	0.0
	TOTAL PP	232	59	25.4
	TOTAL ICD	334	76	22.7

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PRODUCED BY SAB/DPM - TAPS 2805 (A)

(NUMBER & PERCENTAGES) NIH EMPLOYEES AS OF SEPTEMBER 1989, BY ICD, PP, AND GRADE
ICD: NEI

PP	GRADE	TOTAL EMPLOYMENT	NO. OF MINORITIES	PERCENT OF TOTAL
CC	05	1	0	0.0
	06	2	0	0.0
	TOTAL PP	3	0	0.0
ES	01	1	0	0.0
	04	6	1	16.6
	05	1	0	0.0
	TOTAL PP	8	1	12.5
GM	13	5	1	20.0
	14	11	2	18.1
	15	15	1	6.6
	TOTAL PP	31	4	12.9
GS	03	1	0	0.0
	05	2	1	50.0
	06	6	2	33.3
	07	25	7	28.0
	08	3	1	33.3
	09	19	4	21.0
	10	1	0	0.0
	11	10	3	30.0
	12	16	2	12.5
	13	13	2	15.3
	14	8	1	12.5
	15	2	0	0.0
	TOTAL PP	106	23	21.6
	TOTAL ICD	148	28	18.9

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PRODUCED BY SAB/DPM - TAPS 2805 (A)

(NUMBER & PERCENTAGES)

NIH EMPLOYEES AS OF SEPTEMBER 1989, BY ICD, PP, AND GRADE
ICD: NIEHS

PP	GRADE	TOTAL EMPLOYMENT	NO. OF MINORITIES	PERCENT OF TOTAL
CC	03	1	0	0.0
	04	3	0	0.0
	05	3	0	0.0
	06	6	0	0.0
	08	1	0	0.0
	TOTAL PP	14	0	0.0
ES	03	1	0	0.0
	04	9	0	0.0
	TOTAL PP	10	0	0.0
GM	13	26	1	3.8
	14	39	3	7.6
	15	26	1	3.8
	TOTAL PP	91	5	5.4
GS	04	15	8	53.3
	05	38	12	31.5
	06	48	22	45.8
	07	53	17	32.0
	08	4	2	50.0
	09	93	18	19.3
	10	2	1	50.0
	11	46	10	21.7
	12	33	7	21.2
	13	26	4	15.3
	14	8	1	12.5
	15	1	0	0.0
	TOTAL PP	367	102	27.7
	TOTAL ICD	482	107	22.1

04-11-90
PRODUCED BY SAB/DPM - TAPS 2805 (A)

(NUMBER & PERCENTAGES) NIH EMPLOYEES AS OF SEPTEMBER 1989, BY ICD, PP, AND GRADE
ICD: NIA

PP	GRADE	TOTAL EMPLOYMENT	NO. OF MINORITIES	PERCENT OF TOTAL
CC	05	4	1	25.0
	06	13	0	0.0
	07	1	0	0.0
	TOTAL PP	18	1	5.5
ES	01	1	0	0.0
	03	1	0	0.0
	04	6	0	0.0
	TOTAL PP	8	0	0.0
GM	13	25	2	8.0
	14	12	0	0.0
	15	21	1	4.7
	TOTAL PP	58	3	5.1
GS	04	5	3	60.0
	05	20	8	40.0
	06	31	9	29.0
	07	25	8	32.0
	08	5	0	0.0
	09	36	8	22.2
	11	36	4	11.1
	12	28	2	7.1
	13	7	0	0.0
	14	9	0	0.0
	TOTAL PP	202	42	20.7
	TOTAL ICD	286	46	16.0

04-11-90
PRODUCED BY SAB/DPM - TAPS 2805 (A)

(NUMBER & PERCENTAGES)

NIH EMPLOYEES AS OF SEPTEMBER 1989, BY ICD, PP, AND GRADE
ICD: NIAMS

PP	GRADE	TOTAL EMPLOYMENT	NO. OF MINORITIES	PERCENT OF TOTAL
CC	05	1	0	0.0
	06	6	0	0.0
	TOTAL PP	7	0	0.0
ES	04	2	0	0.0
	05	1	0	0.0
	TOTAL PP	3	0	0.0
GM	13	1	0	0.0
	14	7	0	0.0
	15	7	1	14.2
	TOTAL PP	15	1	6.6
GS	04	1	1	100.0
	05	2	2	100.0
	06	7	4	57.1
	07	18	5	27.7
	08	4	0	0.0
	09	3	0	0.0
	11	6	2	33.3
	12	9	1	11.1
	13	3	1	33.3
	14	3	0	0.0
	15	3	1	33.3
	TOTAL PP	59	17	28.8
	TOTAL ICD	84	18	21.4

04-11-90
PRODUCED BY SAB/DPM - TAPS 2805 (A)

(NUMBER & PERCENTAGES) NIH EMPLOYEES AS OF SEPTEMBER 1989, BY ICD, PP, AND GRADE
ICD: NIDCD

PP	GRADE	TOTAL EMPLOYMENT	NO. OF MINORITIES	PERCENT OF TOTAL
ES	04	2	0	0.0
	TOTAL PP	2	0	0.0
GM	13	2	0	0.0
	14	2	0	0.0
	15	2	0	0.0
	TOTAL PP	6	0	0.0
GS	05	3	2	66.6
	06	2	0	0.0
	07	4	1	25.0
	08	1	0	0.0
	09	4	2	50.0
	11	6	0	0.0
	12	1	0	0.0
	13	3	0	0.0
	14	3	0	0.0
	TOTAL PP	27	5	18.5
	TOTAL ICD	35	5	14.2

04-11-90
PRODUCED BY SAB/DPM - TAPS 2805 (A)

(NUMBER & PERCENTAGES)

NIH EMPLOYEES AS OF SEPTEMBER 1989, BY ICD, PP, AND GRADE
ICD: DRR

PP	GRADE	TOTAL EMPLOYMENT	NO. OF MINORITIES	PERCENT OF TOTAL
CC	02	1	1	100.0
	04	1	0	0.0
	05	1	0	0.0
	06	5	0	0.0
	TOTAL PP	8	1	12.5
ES	04	2	0	0.0
	TOTAL PP	2	0	0.0
GM	13	5	2	40.0
	14	12	2	16.6
	15	6	2	33.3
	TOTAL PP	23	6	26.0
GS	04	3	3	100.0
	05	5	4	80.0
	06	14	4	28.5
	07	14	5	35.7
	08	2	0	0.0
	09	4	1	25.0
	11	3	1	33.3
	12	10	7	70.0
	13	3	0	0.0
	14	1	0	0.0
	TOTAL PP	59	25	42.3
	TOTAL ICD	92	32	34.7

04-11-90
PRODUCED BY SAB/DPM - TAPS 2805 (A)

(NUMBER & PERCENTAGES) NIH EMPLOYEES AS OF SEPTEMBER 1989, BY ICD, PP, AND GRADE
ICD: NCNR

PP	GRADE	TOTAL EMPLOYMENT	NO. OF MINORITIES	PERCENT OF TOTAL
CC	04	1	0	0.0
	TOTAL PP	1	0	0.0
ES	03	1	0	0.0
	TOTAL PP	1	0	0.0
GM	13	2	0	0.0
	14	4	0	0.0
	15	1	0	0.0
	TOTAL PP	7	0	0.0
GS	05	2	1	50.0
	06	1	0	0.0
	07	4	1	25.0
	09	3	0	0.0
	12	3	0	0.0
	13	4	0	0.0
	14	1	0	0.0
	TOTAL PP	18	2	11.1
	TOTAL ICD	27	2	7.4

04-11-90
PRODUCED BY SAB/DPM - TAPS 2805 (A)

(NUMBER & PERCENTAGES)

NIH EMPLOYEES AS OF SEPTEMBER 1989, BY ICD, PP, AND GRADE
ICD: JEFIC

PP	GRADE	TOTAL EMPLOYMENT	NO. OF MINORITIES	PERCENT OF TOTAL
CC	06	3	1	33.3
	TOTAL PP	3	1	33.3
ES	04	1	0	0.0
	TOTAL PP	1	0	0.0
GM	13	1	0	0.0
	14	4	0	0.0
	15	6	0	0.0
	TOTAL PP	11	0	0.0
GS	02	1	1	100.0
	04	5	3	60.0
	05	5	0	0.0
	06	5	1	20.0
	07	8	0	0.0
	08	1	0	0.0
	09	4	0	0.0
	11	3	0	0.0
	12	5	0	0.0
	13	4	0	0.0
	14	1	0	0.0
	15	1	0	0.0
	TOTAL PP	43	5	11.6
	TOTAL ICD	58	6	10.3

04-11-90
PRODUCED BY SAB/DPM - TAPS 2805 (A)

(NUMBER & PERCENTAGES) NIH EMPLOYEES AS OF SEPTEMBER 1989, BY ICD, PP, AND GRADE
ICD: NLM

PP	GRADE	TOTAL EMPLOYMENT	NO. OF MINORITIES	PERCENT OF TOTAL
CC	05	1	0	0.0
	06	3	0	0.0
	TOTAL PP	4	0	0.0
ES	03	1	0	0.0
	04	5	1	20.0
	05	1	0	0.0
	TOTAL PP	7	1	14.2
GM	13	20	3	15.0
	14	18	1	5.5
	15	26	3	11.5
	TOTAL PP	64	7	10.9
GS	02	1	1	100.0
	03	3	0	0.0
	04	18	12	66.6
	05	43	18	41.8
	06	37	11	29.7
	07	51	26	50.9
	08	18	8	44.4
	09	27	9	33.3
	10	3	2	66.6
	11	68	16	23.5
	12	79	18	22.7
	13	51	6	11.7
	14	17	1	5.8
	15	2	0	0.0
	TOTAL PP	418	128	30.6
	TOTAL ICD	493	136	27.5

04-11-90
PRODUCED BY SAB/DPM - TAPS 2805 (A)

(NUMBER & PERCENTAGES) NIH EMPLOYEES AS OF SEPTEMBER 1989, BY ICD, PP, AND GRADE
ICD: OD

PP	GRADE	TOTAL EMPLOYMENT	NO. OF MINORITIES	PERCENT OF TOTAL
CC	04	2	1	50.0
	05	3	1	33.3
	06	9	0	0.0
	TOTAL PP	14	2	14.2
ES	02	1	0	0.0
	03	1	0	0.0
	04	12	1	8.3
	05	2	0	0.0
	TOTAL PP	16	1	6.2
GM	13	37	3	8.1
	14	44	6	13.6
	15	39	4	10.2
	TOTAL PP	120	13	10.8
GS	02	3	0	0.0
	03	6	3	50.0
	04	30	13	43.3
	05	52	29	55.7
	06	66	29	43.9
	07	116	40	34.4
	08	17	3	17.6
	09	52	12	23.0
	10	7	0	0.0
	11	64	19	29.6
	12	110	27	24.5
	13	84	18	21.4
	14	19	2	10.5
	15	2	0	0.0
	TOTAL PP	628	195	31.0
	TOTAL ICD	778	211	27.1

04-11-90
PRODUCED BY SAB/DPM - TAPS 2805 (A)

(NUMBER & PERCENTAGES)

NIH EMPLOYEES AS OF SEPTEMBER 1989, BY ICD, PP, AND GRADE
ICD: ORS

PP	GRADE	TOTAL EMPLOYMENT	NO. OF MINORITIES	PERCENT OF TOTAL
CC	02	2	0	0.0
	03	4	0	0.0
	04	4	0	0.0
	05	11	0	0.0
	06	6	1	16.6
	TOTAL PP	27	1	3.7
ES	04	1	0	0.0
	TOTAL PP	1	0	0.0
GM	13	8	2	25.0
	14	16	1	6.2
	15	9	2	22.2
	TOTAL PP	33	5	15.1
GS	01	1	0	0.0
	02	2	1	50.0
	03	3	1	33.3
	04	72	48	66.6
	05	87	54	62.0
	06	45	22	48.8
	07	50	23	46.0
	08	6	4	66.6
	09	38	15	39.4
	10	2	1	50.0
	11	50	13	26.0
	12	40	13	32.5
	13	45	12	26.6
	14	9	1	11.1
	TOTAL PP	450	208	46.2
	TOTAL ICD	511	214	41.8
	TOTAL NIH	10,372	2,529	24.3

04-11-90
PRODUCED BY SAB/DPM - TAPS 2805 (A)

(NUMBER & PERCENTAGES)

NIH EMPLOYEES AS OF SEPTEMBER 1989, BY ICD, PP, AND GRADE
ICD: DRS

PP	GRADE	TOTAL EMPLOYMENT	NO. OF MINORITIES	PERCENT OF TOTAL
CC	03	6	3	50.0
	04	7	0	0.0
	05	5	2	40.0
	06	6	2	33.3
	07	1	0	0.0
	TOTAL PP	25	7	28.0
ES	04	1	0	0.0
	TOTAL PP	1	0	0.0
GM	13	8	2	25.0
	14	6	1	16.6
	15	6	0	0.0
	TOTAL PP	20	3	15.0
GS	03	4	0	0.0
	04	21	10	47.6
	05	21	10	47.6
	06	37	19	51.3
	07	31	13	41.9
	08	5	1	20.0
	09	19	12	63.1
	10	4	1	25.0
	11	38	6	15.7
	12	29	8	27.5
	13	12	2	16.6
	14	10	1	10.0
	15	1	0	0.0
	TOTAL PP	232	83	35.7
	TOTAL ICD	278	93	33.4

04-11-90
PRODUCED BY SAB/DPM - TAPS 2805 (A)

(NUMBER & PERCENTAGES) NIH EMPLOYEES AS OF SEPTEMBER 1989, BY ICD, PP, AND GRADE
ICD: CC

PP	GRADE	TOTAL EMPLOYMENT	NO. OF MINORITIES	PERCENT OF TOTAL
CC	01	2	0	0.0
	02	4	1	25.0
	03	27	7	25.9
	04	52	7	13.4
	05	49	5	10.2
	06	32	2	6.2
	TOTAL PP	166	22	13.2
ES	02	1	0	0.0
	04	1	0	0.0
	05	1	0	0.0
	TOTAL PP	3	0	0.0
GM	13	16	2	12.5
	14	4	2	50.0
	15	14	1	7.1
	TOTAL PP	34	5	14.7
GS	02	3	3	100.0
	03	13	8	61.5
	04	53	41	77.3
	05	144	97	67.3
	06	97	59	60.8
	07	109	34	31.1
	08	59	17	28.8
	09	287	65	22.6
	10	351	41	11.6
	11	235	47	20.0
	12	126	17	13.4
	13	15	1	6.6
	14	12	1	8.3
	15	2	0	0.0
	TOTAL PP	1,506	431	28.6
	TOTAL ICD	1,709	458	26.7

04-11-90
PRODUCED BY SAB/DPM - TAPS 2805 (A)

(NUMBER & PERCENTAGES) NIH EMPLOYEES AS OF SEPTEMBER 1989, BY ICD, PP, AND GRADE
ICD: DRG

PP	GRADE	TOTAL EMPLOYMENT	NO. OF MINORITIES	PERCENT OF TOTAL
CC	04	1	0	0.0
	05	1	0	0.0
	06	7	0	0.0
	07	1	0	0.0
	TOTAL PP	10	0	0.0
ES	01	1	0	0.0
	04	1	0	0.0
	TOTAL PP	2	0	0.0
GM	13	12	5	41.6
	14	95	15	15.7
	15	24	2	8.3
	TOTAL PP	131	22	16.7
GS	02	5	2	40.0
	03	9	2	22.2
	04	30	14	46.6
	05	48	24	50.0
	06	25	12	48.0
	07	70	23	32.8
	08	20	3	15.0
	09	21	7	33.3
	10	1	0	0.0
	11	11	2	18.1
	12	27	5	18.5
	13	13	1	7.6
	14	3	0	0.0
	TOTAL PP	283	95	33.5
	TOTAL ICD	426	117	27.4

04-11-90
PRODUCED BY SAB/DPM - TAPS 2805 (A)

(NUMBER & PERCENTAGES) NIH EMPLOYEES AS OF SEPTEMBER 1989, BY ICD, PP, AND GRADE
ICD: DCRT

PP	GRADE	TOTAL EMPLOYMENT	NO. OF MINORITIES	PERCENT OF TOTAL
CC	05	4	0	0.0
	06	3	0	0.0
	TOTAL PP	7	0	0.0
ES	04	4	0	0.0
	TOTAL PP	4	0	0.0
GM	13	9	1	11.1
	14	16	1	6.2
	15	8	1	12.5
	TOTAL PP	33	3	9.0
GS	03	2	1	50.0
	04	15	8	53.3
	05	17	9	52.9
	06	9	4	44.4
	07	29	10	34.4
	08	17	12	70.5
	09	19	4	21.0
	11	29	9	31.0
	12	45	9	20.0
	13	50	3	6.0
	14	18	1	5.5
	15	1	0	0.0
	TOTAL PP	251	70	27.8
	TOTAL ICD	295	73	24.7

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

FY 1991 Budget — Page No.

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Authorizing legislation.....

Appropriations history.....

Justification:

A. General statement.....
B. Program accomplishments.....
C. AIDS construction program.....
D. Research facilities.....
E. Service and administrative facilities.....

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

For construction of, and acquisition of equipment for, facilities of or used by the National Institutes of Health, [$61,600,000] *$88,600,000*, to remain available until expended.

(Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 1990.)

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

Amounts Available for Obligation 1/

	1989 Actual	1990 Appropriation	1991 Estimate
Appropriation.....	$39,000,000	$61,600,000	$88,600,000
Enacted admin. reduction..	-468,000	—	—
Sequestar order.....	—	-558,000	—
Subtotal, adjusted appropriation.....	38,532,000	61,042,000	88,600,000
Real transfer to the Health Resources and Services Administration for AZT grants.....	-40,000	—	—
Subtotal, adjusted budget authority.....	38,492,000	61,042,000	88,600,000
Unobligated balance, start of year.....	49,360,000	63,634,000	—
Unobligated balance, end of year.....	-63,634,000	—	—
Total obligations....	24,218,000	124,676,000	88,600,000

1/ Excludes the following amount for reimbursable activities carried out by this account: 1989 — $256,000.

Buildings and Facilities

Summary of Changes

1990 Estimated budget authority	$61,042,000
1991 Estimated budget authority	88,600,000
Net change	+27,558,000

Increases:

A. Program:

1.	Infrastructure Modernization & Improvement Program	+$19,200,000
2.	Clinical Center Modernization	+14,500,000
3.	Rehabilitation of Laboratory Buildings 2, 3, 4, 5, 7, and 8	+13,000,000
4.	Intramural Animal Facilities	+18,500,000
5.	AIDS Facilities	+16,500,000
6.	Repairs and Improvements	+6,900,000
	Total increases	+88,600,000

Decreases:

A. Program:

1.	Clinical Center Modernization	-$1,800,000
2.	Intramural Animal Facilities	-5,300,000
3.	Child Health and Neurosciences Facilities	-33,000,000
4.	Additions at NIEHS	-20,000
5.	AIDS Facilities	-14,765,000
6.	Repairs and Improvements	-6,157,000
	Total decreases	-61,042,000
Total, net change		+27,558,000

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

Budget Authority by Activity
(Dollars in thousands)

	1989 Actual	1990 Appropriation	1991 Estimate
Research facilities	$18,180	$97,546	$62,500
Service and administrative facilities	6,038	27,130	26,100
Total obligations	24,218	124,676	88,600
Unobligated balance, start of year	-49,360	-63,634	---
Unobligated balance, end of year	63,634	---	---
Total budget authority	38,492	61,042	88,600
HIV/AIDS	(4,900)	(14,765)	(16,500)

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

Budget Authority by Object

	1990 Appropriation	1991 Estimate	Increase or Decrease
Other services	$60,922,000	$88,480,000	+$27,558,000
(Obligations)	(124,556,000)	88,480,000	-36,076,000
Supplies and materials	20,000	20,000	---
(Obligations)	(20,000)	(20,000)	---
Equipment	100,000	100,000	---
(Obligations)	(100,000)	(100,000)	---
Total budget authority by object	61,042,000	88,600,000	+27,558,000
(Total obligations by object)	(124,676,000)	(88,600,000)	(-36,076,000)

Buildings and Facilities

Significant Item in House Appropriations Committee Report

Item	Action Taken or to be Taken
1990 House Report	
Animal Facilities	
1. The Committee is particularly supportive, however, of efforts to upgrade the quality of animal facilities at NIH and expects a substantial amount of these funds to be allocated in this area.	A substantial portion of the available FY 1990 appropriation will be used to further upgrade animal facilities at the NIH. The NIH is continuing to review needs for animal facilities improvements to achieve campus-wide AAALAC accreditation and maintain accreditation in the central NIH animal facilities.

Buildings and Facilities

Significant Items in Senate Appropriations Committee Report

Item	Action Taken or to be Taken
1990 Senate Report	
NIEHS Facilities	
1. The Committee is well aware of the need for NIEHS to begin efforts to obtain a new facility to house its intramural activities. In view of the expiring lease on current facilities and the disinterest and unwillingness to extend the lease, NIH management needs to address this issue carefully in time for a full presentation and budget request for the fiscal year 1991 hearings. The Committee would like a report including recommendations and appropriate funding recommendations for the future facilities needs of the NIEHS.	The NIH will provide a report on NIEHS facility needs to the Committee prior to the hearings. It will address the problem concerning the lease renewals and the need for a major facility addition.
Buildings and Facilities Construction Program	
2. The buildings and facilities appropriation supports several ongoing NIH construction projects....The Committee has added $20,000,000 over the amount requested...$3,500,000 of which the Committee expects to be used for the Animal Facilities Improvement Program and $10,000,000 for the consolidated office building.	Currently an Environmental Assessment of the Consolidated Office Building (COB) is being prepared and we hope to let a design contract this fiscal year. After providing funds for the next phase of construction of the Child Health and Neurosciences Building, as suggested in the Conference Report, insufficient funds are available for the Phase I construction of the COB. A substantial portion of the remaining FY 1990 Buildings and Facilities funds will be used for the Animal Facilities Improvement Program.

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1990 Amount Authorized	1990 Appropriation	1991 Amount Authorized	1991 Budget Estimate
Funded Authorizations:						
Buildings and Facilities.....	Title IV, Section 402(b)	408282	Indefinite	$61,042,000	Indefinite	$88,600,000
Total Budget Authority..				61,042,000		88,600,000

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NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

Appropriations History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1982	$10,310,000	$10,310,000	$10,310,000	$9,898,000
1983	17,500,000	17,500,000	17,500,000	17,500,000
1984	19,900,000	24,980,000	25,100,000	25,040,000
1985	11,100,000	21,730,000	21,700,000	21,730,000
1986	14,900,000	14,900,000	14,900,000	14,900,000
1986 Sequestar				-641,000
1987	8,000,000	31,900,000	31,900,000	31,900,000
1988	5,000,000	30,000,000	50,000,000	47,870,000
1989	5,000,000	20,000,000	12,500,000	38,532,000
1990	1,600,000	81,600,000	41,600,000	61,600,000
1990 Sequestar				-558,000
1991	88,600,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

Justification

Buildings and Facilities

	1990 Appropriation	1991 Estimate	Increase or Decrease
Research facilities.....	$54,885,000	$62,500,000	+$7,615,000
Service and administrative facilities.....	6,157,000	26,100,000	+19,943,000
TOTAL.....	61,042,000	88,600,000	+27,558,000
HIV/AIDS.....	(14,765,000)	(16,500,000)	(+1,735,000)

General Statement

This appropriation provides for the design, construction, improvements and major repair of clinical and laboratory buildings and supporting facilities essential to the mission of the National Institutes of Health. Funds are provided for non-recurring direct construction projects, as well as ongoing major repairs and improvements. All funds are available until expended.

Buildings and facilities funded under this appropriation include those required for both research programs and support services at the main NIH Reservation in Bethesda, Maryland, totaling 60 buildings and more than six million gross square feet of space. Additional facilities are the NIH Animal Center located in Poolesville, Maryland; the NIEHS facility in Research Triangle Park, North Carolina; the Rocky Mountain Laboratory, Hamilton, Montana; the Gerontology Research Facility, Baltimore, Maryland; Primate Facilities at Perrine, Florida; New Iberia, Louisiana; and Sabana Seca, Puerto Rico; the Frederick Cancer Research Facility, Frederick, Maryland; and other NIH field stations.

Overall Budget Policy

Reflecting the high priority placed on biomedical research by the Secretary, the 1991 budget request for Buildings and Facilities is $88,600,000. It is focused on the revitalization of the NIH campus and provides for the initial funding of infrastructure modernization and improvement at the NIH, the continuation of the Clinical Center modernization, the rehabilitation of older laboratory buildings, the renovation of animal facilities, and renovation and construction related to AIDS research. The request level also provides for the routine repair and improvement of facilities.

Program Accomplishments

Construction of facilities for the National Institutes of Health spans a period of more than 50 years, dating back to legislation which authorized Building 1 in June 1936. At present, facilities programs include the infrastructure modernization and improvement program; the modernization of the Clinical Center; the rehabilitation of older laboratory buildings; the renovations of existing animal facilities; construction of the Child Health and Neurosciences Facilities; planning and design of the Consolidated Office Building; design of additions at the NIEHS in North Carolina; and AIDS-related construction and renovations.

The NIH has developed an infrastructure modernization and improvement program (IMIP) to carry out the replacement and expansion of the central plant equipment and utility distribution systems, the majority of which are from 20 to 40 years old. The primary goals are to (1) correct safety deficiencies, (2) restore and improve reliability of the utility systems for dependable service, (3) expand capacity of the mechanical and electrical utility systems to meet current and future demands for services, and (4) improve the efficiency of the utility systems to extend their useful life and conserve energy and costs. Major infrastructure deficiencies include refrigeration equipment age and capacity limitations; boiler equipment age; deterioration of steam and chilled water distribution piping; environmental and safety hazards connected with the distribution of electricity and steam, use of PCB containing transformers, and the widespread presence of asbestos as an insulating material; and excessive operating costs. Less critical but significant problems existing in other central utility systems will be studied, e.g. electrical distribution, potable water, sanitary and storm sewer, and central air systems.

The modernization of the Clinical Center began in 1979 as a multiyear program to accommodate safety requirements, modern procedures, equipment and facilities for the delivery of quality patient care and supporting research. The modernization program consists of about 50 projects of substantive scope. Projects under construction or recently completed are patient care units on floors 10, 12, 13 West and 2 East; Phase I of the fire safety program (areas of refuge); a new surgical intensive care unit; relocation of the Pharmacy and central sterile supply; renovation of 6 East rehabilitation medicine; a dental clinic; a medical records department; a nuclear magnetic resonance facility; a surgical facility for cardiac and neurosurgery; and renovations to the 14th floor patient support space and medical information systems. Design is proceeding on the automatic sprinkler system for the entire Building 10 Complex and emergency replacement of an existing supply and exhaust system serving one wing of Building 10.

The long-range goal of the Buildings and Facilities Program provides for the major renovation of six laboratory buildings that have been operational for approximately 45 years. The buildings, in order of renovation, are 8, 4, 5, 2, 3, and 7. Although the exterior of the buildings are structurally sound, the building support systems and interior architectural features and layouts have become obsolete. As each building is completed, the programs in the next building to be renovated are moved into the newly renovated space. Building 8, the initial building renovated, was completed in March 1986. The

programs in Building 4 were moved to Building 8 and Building 4 was completed in August 1988. Programs in Building 5 have been moved to Building 4. Phase I construction of Building 5 began in July 1989 and will be completed by May 1990.

The initial phase of the NIH plan for upgrading intramural animal facilities involves constructing new buildings, 6B on the NIH campus and 116A at the NIH Animal Center at Poolesville, Maryland; major renovations in Buildings 10A and 36; and smaller renovations in Buildings 7, 14D, 29A, 30, and 41. All of these projects are complete or will be completed in early fiscal year 1990.

The entire Child Health and Neurosciences Facilities program consists of construction of Building 49, related building expansions, and extensive utility upgrades. Construction is proceeding on Building 49 foundations and related site utilities. Funds appropriated thus far allow for the completion of Phase III of construction of Building 49 (exterior walls, major mechanical and electrical systems and central animal facilities), the design of the Building 30 Tower, the completion of the interior and the construction of the laboratories in Building 6B, and the upgrading required for the related utility systems.

Funds have been appropriated for the planning and design of the new Consolidated Office Building which will serve as a Center for Biomedical Research Management. Completion of planning and design will be contingent upon results of an environmental assessment currently underway. The building, at its full scope, will be constructed on the NIH campus. It will contain about 700,000 gross square feet and accommodate approximately 3,000 people at a cost of $119 million in 1990 dollars. This facility will provide office and support space for scientists and administrative staff who manage most of the NIH extramural programs inclusive of the AIDS program, scientists who guide the peer review groups, and support staff responsible for fiscal and other administrative aspects of grants and research contracts. The facility will provide for more efficient operation and management of the NIH extramural programs.

The continuing program of repairs and improvements includes activities of a routine nature that are required as the result of constant use, exposure to the elements, and changes in space utilization. Such activities normally involve the repair and improvement to central plant utility systems, building structures and systems; repair to roads, sidewalks and parking areas; fire and safety improvements; replacement of elevators and roofs; energy conservation improvements; and accommodations for the handicapped.

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AIDS Construction Program

B&F AIDS Program

Funds have been provided for the renovation, modernization, and expansion of existing facilities and the design and construction of new facilities related to AIDS research activities. The most critical concerns at the NIH are the provision of high-level biocontainment facilities to enhance safety in the workplace; the consolidation of currently dispersed laboratories to improve communications and efficiency among the many scientists involved in the program; the alleviation in scientific areas of overcrowding; the creation of a modern, consolidated facility for the primates so essential in vaccine and drug development; and the accommodation of increasing numbers of inpatients requiring intensive care.

Recent Accomplishments

Projects which are currently being designed or constructed include an addition to the Clinical Center, renovating the Twinbrook II Building to house key components of the NIAID AIDS research program, and a new building for NCI at the Frederick Cancer Research Facility.

Future Plans

Planned projects include a retrovirus laboratory, a primate facility, an expanded medical intensive care unit in the Clinical Center to accommodate AIDS patients, and various renovations to existing AIDS laboratories. Because of the rapidly changing requirements of the AIDS research program, there may be adjustments to this construction plan.

Buildings and Facilities

Research Facilities

Authorization: Indefinite

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$54,885,000	$62,500,000	+$7,615,000

Purpose and Method of Operation

This activity provides for the design and construction of facilities for the NIH research programs. Ongoing construction projects within this activity include the continuing renovation of the Clinical Center; the renovation of six of the campus' older laboratory buildings; consolidation, renovation, and construction of existing animal facilities; and the Child Health and Neurosciences Facilities. Design is essentially complete for replacement facilities of those leased by the National Institute of Environmental Health Sciences.

Rationale for the Budget Request

The basic thrusts of the 1991 budget request are to improve safety, reduce obsolescence to allow state-of-the-art research, and to bring the care and use of animals into compliance with AAALAC standards. The 1991 estimate for Research Facilities is $62,500,000. It provides for continuation of the Clinical Center modernization and safety improvements, rehabilitation of laboratory buildings, and renovation and construction of intramural animal and AIDS facilities. Potential out-year costs are given in 1991 dollars. Estimates will be refined as the projects proceed through the planning and design stages.

Clinical Center Modernization

1991 Budget Request..... $14,500,000

The orientation of the Clinical Center modernization project was reevaluated and has been modified to focus on safety concerns, the central building utilities, reducing the costs of the project, and maintaining accreditation with the Joint Commission on Accreditation of Health Care Organizations (JCAHO). The 1991 request will fund facility improvements required for safety and to maintain the hospital's accreditation (Phase II sprinklers and Phase I fire alarm replacement), the renovation of two 40-year old air conditioning systems serving 23 patient care units; and a portion of the requirement to design and construct a new and expanded Medical Intensive Care Unit. Potential out-year costs of this project total $25 million.

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Rehabilitation of Laboratory Buildings

1991 Budget Request..... $13,000,000

In 1991, funds are requested to provide for the completion of the Building 5 construction and the design of Building 2 as part of the long-term rehabilitation effort. Modernization is required to assure a safe operating environment for state-of-the-art research; to provide structures that meet new life safety codes; and provide for the needs of the handicapped, revised levels of air purity and temperature stability, energy conservation and other requirements of modern biomedical research. While one building is being renovated, the next building is being designed for renovation.

The renovation of Building 8 was completed in March 1986 and the Building 4 construction was completed in August 1988. Construction of Building 5 is proceeding, with completion of Phase I anticipated by May 1990. Buildings 2, 3, and 7 remain to be rehabilitated. Potential out-year costs of this project total $52.1 million.

Intramural Animal Facilities

1991 Budget Request..... $18,500,000

The NIH is currently involved in a significant program to ensure that all animal facilities on the NIH campus meet American Association for Accreditation of Laboratory Animal Care (AAALAC) standards. This has grown from the increased public concern over the care and use of animals in research and NIH's concern that its own facilities meet AAALAC guidelines for the housing and use of animals in research. Funds in 1991 will provide for the construction or upgrade of the central NIH animal facilities, Buildings 14 and 28 at the NIH, and facilities at the NIH Animal Center. Potential out-year costs of this project total $25.2 million.

AIDS Facilities

1991 Budget Request..... $16,500,000

The 1991 request includes funds to complete the renovations at the Twinbrook II Building to house an important portion of the NIAID AIDS research program, the construction of a new primate facility for AIDS research, and renovation or expansion of NCI AIDS laboratories.

Buildings and Facilities

Service and Administrative Facilities

Authorization: Indefinite

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$6,157,000	$26,100,000	+$19,943,000

Purpose and Method of Operation

This activity includes the continuing program of repairs and improvements to existing buildings and facilities, and to those under design or construction that house research and administrative activities. This activity also provides for the design and construction of new facilities for the NIH service and administrative programs including funds for the planning and design of the Consolidated Office Building.

Rationale for the Budget Request

This activity is critical to the continued usage of the NIH research facilities. The 1991 estimate for Service and Administrative Facilities is $26,100,000. It provides for continuation of the program of repairs and improvements to existing facilities and implementation of the infrastructure modernization and improvement program at NIH.

Infrastructure Modernization and Improvement Program

1991 Budget Request..... $19,200,000

The Infrastructure Modernization and Improvement Program is the most critical construction activity in this budget. The central plant equipment and distribution system at the NIH are in need of major programmed modernization and expansion to ensure the proper support for the continuance of the NIH biomedical research mission. The total cost will exceed $150 million over a ten-year period, excluding facilities planned or under construction and specific building infrastructure improvements.

The 1991 request will provide for the installation of a fifth boiler, enhancement of two chillers, design for the underground utility expansion and central utility tunnel, and completion of replacement of PCB transformers.

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Repairs and Improvements

1991 Budget Request..... $6,900,000

The Repairs and Improvements program applies to the physical plants at Bethesda, Poolesville, and Baltimore, Maryland; Research Triangle Park, North Carolina; Hamilton, Montana; Perrine, Florida; and other field stations for which NIH has the property holding responsibility. Program-related improvements are required to accommodate changes in the direction of research efforts.

Some of these costs are for items such as roofs, roads, and underground utilities that require major repair or improvement in order to retain or achieve sound operating conditions. Others are largely non-recurring purchases of equipment or parts that require unpredictable replacement or repair. Activities supported with these funds are relatively small and unanticipated to the extent that lead time is not sufficient to request funds during the regular budget cycle.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Office of the Director

FY 1991 Budget

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NATIONAL INSTITUTES OF HEALTH

Office of the Director

For carrying out the responsibilities of the Office of the Director, National Institutes of Health, [$108,987,000] *$82,975,000* including purchase of not to exceed five passenger motor vehicles for replacement only: *Provided*, That [$34,000,000 of this amount shall be available only for the purchase of an advanced design supercomputer: *Provided further*, That in addition, the Secretary shall transfer $15,000,000 from appropriations available to each of the Institutes which shall be available for extramural facilities construction grants if authorized in law and if awarded competitively including such amounts as he may deem appropriate for research animal production facilities] *the Director may direct up to one percent of the total amount made available in this Act to all National Institutes of Health appropriations to high-priority activities the Director may so designate: Provided further, That no such appropriation shall be increased or decreased by more than one percent by any such transfers and that the Congress is promptly notified of the transfer: Provided further, That the Director is authorized to establish ten endowed chairs, to be filled by eminent senior biomedical scientists for periods up to five years, within the organizational structure of the intramural research programs of the National Institutes of Health: Provided further, That the Director may collect non-Federal funds, to remain available until expended, to supplement the Federal salaries of said chairs: Provided further, That these salary augmentations may not result in the total compensation of these scientists exceeding 150 percent of the Executive Level II: Provided further, That this increment above the Federal salary of these scientists is derived solely from the non-Federal funds*

collected by the Director: Provided further, That this increment above the Federal salary of these scientists is deemed compensation for tax purposes but not for purposes of Subpart G of Title 5, U.S.C.

(Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 1990.)

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Language Analysis

Language Provision	Explanation
"....the Director may direct up to one percent of the total amount made available in this Act to all National Institutes of Health appropriations to high-priority activities the Director may so designate: Provided further, that no such appropriation shall be increased or decreased by more than one percent by any such transfers and that the Congress is promptly notified of the transfer...."	The budget proposes to give the NIH Director the discretion to direct up to one percent of NIH appropriations to emerging activities.
"....the Director is authorized to establish ten endowed chairs, to be filled by eminent senior biomedical scientists for periods up to five years, within the organizational structure of the intramural research programs of the National Institutes of Health: Provided further, that the Director may collect non-Federal funds, to remain available until expended, to supplement the Federal salaries of said chairs: Provided further, that these salary augmentations may not result in the total compensation of these scientists exceeding 150 percent of Executive Level II: Provided further, that this increment above the Federal salary of these scientists is derived solely from the non-Federal funds collected by the Director; Provided further, that this increment above the Federal salary of these scientists is deemed compensation for tax purposes but not for purposes of Subpart G of Title 5, U.S.C...."	Consistent with recommendations made by a recent Institute of Medicine report, the budget proposes the establishment of ten endowed chairs. The chairs would be supported through Federal funds and private donations, and be used to support term appointments of distinguished scientists from the extramural research community at the NIH.

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Amounts Available for Obligation 1/

	1989 Actual	1990 Appropriation	1991 Estimate
Appropriation	$73,078,000	$108,987,000	$82,975,000
Enacted administrative reduction	-877,000	-519,000	...
Sequester order	...	-1,049,000	...
Subtotal, adjusted appropriation	72,201,000	107,419,000	82,975,000
Real transfer to the Health Resources and Services Administration for AZT grants	-125,000	...	...
Comparative transfer to:			
National Center for Human Genome Research	-661,000	...	...
Institutes and Divisions of the National Institutes of Health for Non-AIDS and AIDS FTEs	-9,366,000	...	...
Division of Research Resources for the RCMI Program	-15,312,000	-17,503,000	...
Subtotal, adjusted budget authority	46,737,000	89,916,000	82,975,000
Unobligated balance lapsing	-5,000	...	...
Total obligations	46,732,000	89,916,000	82,975,000

1/ Excludes the following amounts for reimbursable activities carried out under this account: 1989 - $30,404,000; 1990 - $33,530,000; 1991 - $33,530,000 and $341,000 for royalties received in 1989. The 1990 appropriation and 1991 estimate excludes $200,000 in permanent budget authority expected to be realized from Cooperative Research and Development Agreements.

NATIONAL INSTITUTES OF HEALTH

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Budget Mechanism
(Dollars in thousands)

	1989 Actual		1990 Appropriation		1991 Estimate	
	FTEs	Amount	FTEs	Amount	FTEs	Amount
Research Management and Support	558	$46,737	601	$89,916	612	$82,975
Director's Discretionary Fund		---		---		(20,000)
Academic Research Enhancement Award Program		(10,878)		(11,009)		(11,372)
Intramural Research in Diagnostic Radiology		---		(1,970)		(2,065)
Total Budget Authority	558	46,737	601	89,916	612	82,975
HIV/AIDS	(16)	(5,792)	(35)	(10,551)	(37)	(13,747)

NOTE: The 1989 column has been adjusted for comparability for the transfer of FTEs to the Institutes and Divisions as follows: AIDS FTEs - $5,603,000; Non-AIDS FTEs - $3,763,000. A comparable transfer to the Division of Research Resources for the RCMI program is reflected in 1989 for $15,312,000 and in 1990 for $17,503,000. The 1989 column also reflects a comparable transfer of $661,000 to the National Center for Human Genome Research. The 1990 appropriation and 1991 estimate excludes $200,000 in permanent budget authority expected to be realized from Cooperative Research and Development Agreements.

NATIONAL INSTITUTES OF HEALTH

Office of the Director

CROSSWALK - 1989 Actual

(Dollars in thousands)

PROGRAM ACTIVITY	MECHANISM: Research Management and Support	Total
Research Management and Support	$46,737	$46,737
Total budget authority	46,737	46,737

NATIONAL INSTITUTES OF HEALTH

Office of the Director

CROSSWALK - 1990 Appropriation

(Dollars in thousands)

PROGRAM ACTIVITY	MECHANISM: Research Management and Support	Total
Research Management and Support	$89,916	$89,916
Total budget authority	89,916	89,916

NATIONAL INSTITUTES OF HEALTH

Office of the Director

CROSSWALK - 1991 Estimate

(Dollars in thousands)

PROGRAM ACTIVITY	MECHANISM: Research Management and Support	Total
Research Management and Support	$82,975	$82,975
Total budget authority	82,975	82,975

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Summary of Changes

1990 Estimated Budget Authority	$89,916,000
1991 Estimated Budget Authority	82,975,000
Net Change	-6,941,000

Changes	1990 Current Estimate Base Pos (FTEs)	1990 Current Estimate Base Budget Authority	Change from Base Pos (FTEs)	Change from Base Budget Authority
A Built-in				
1. Within-grade Increase		$28,332,000		+$427,000
2. Annualization of January 1990 Pay Raise		28,332,000		+251,000
3. Cost of January 1991 Pay Raise		28,332,000		+1,146,000
4. One Extra Day of Pay		28,332,000		+113,000
5. Federal Employees Compensation Fund Increase		145,000		+5,000
6. Unemployment Compensation Fund Increase		69,000		+2,000
7. Annualization of 1989 AIDS FTE Increase		266,000		+250,000
8. FTS Rate Increase		199,000		+7,000
9. Increased Cost of Services and Supplies		26,041,000		+930,000
10. Service and Supply Fund Increase		2,020,000		+72,000
11. DHHS Working Capital Fund		157,000		-8,000
Subtotal				+3,195,000
B Program				
1. Expansion of the Office of Scientific Integrity	(6)	600,000	(+9)	+808,000
2. Establishment of NIH Director's Discretionary Fund		---		+20,000,000
3. Increase in Intramural Diagnostic Radiology Program		1,970,000		+30,000
4. Expansion of AIDS Loan Repayment Program		989,000		+978,000
5. Expansion of Intramural Targeted Antiviral Program		6,601,000		+650,000
6. Expansion of Office of AIDS Research	(31)	1,360,000	(+2)	+506,000
7. Increase for NIH AIDS Data Base		839,000		+122,000
8. Increase for AIDS Technology Transfer Meetings		474,000		+260,000
9. Decrease for NIH Supercomputer		33,490,000		-33,490,000
Subtotal	(601)		(+11)	-10,136,000
Total, Changes	(601)		(+11)	-6,941,000

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Budget Authority by Activity
(Dollars in thousands)

	1989 Actual	1990 1/ Appropriation	1991 1/ Estimate
Research Management and Support	$46,737	$89,916	$82,975
Total budget authority	46,737	89,916	82,975

1/ The 1990 appropriation reflects a comparable transfer of $17,503,000 to the Division of Research Resources for the RCMI program. The 1990 appropriation and 1991 estimate excludes $200,000 in permanent budget authority expected to be realized from Cooperative Research and Development Agreements.

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Budget Authority by Object

	1990 Appropriation	1991 Estimate	Increase or Decrease
Total number of full-time permanent positions	582	593	+11
Total compensable workyears: Full-time equivalent employment	613	624	+11
Full-time equivalent of overtime and holiday hours	4	4	---
Average ES salary	$79,100	$96,700	+$17,600
Average GS/GM grade	10	10	---
Average salary, grades established by act of July 1, 1944 (42 USC 207)	$40,956	$42,389	+$1,433
Average salary of ungraded positions	$66,117	$68,431	+$2,314
Personnel Compensation:			
Full-time permanent	$22,682,000	$24,884,000	+$2,202,000
Other than full-time permanent	1,363,000	1,543,000	+180,000
Other personnel compensation	531,000	577,000	+46,000
Special personnel service payments	86,000	92,000	+6,000
Total, personnel compensation	24,662,000	27,096,000	+2,434,000
Personnel benefits	3,670,000	4,049,000	+379,000
Benefits for former personnel	33,000	35,000	+2,000
Travel and transportation of persons	406,000	489,000	+83,000
Transportation of things	48,000	59,000	+11,000
Rent, communications and utilities	719,000	762,000	+43,000
Printing and reproduction	427,000	457,000	+30,000
Other services	57,630,000	47,424,000	-10,206,000
Supplies and materials	345,000	382,000	+37,000
Equipment	1,976,000	2,222,000	+246,000
Total budget authority by object	89,916,000	82,975,000	-6,941,000

Office of the Director

Significant Items in House Appropriations Committee Report

Item	Action Taken or To Be Taken
1990 House Report	
1. Research Centers at Minority Institutions The Committee has included a total of $16.3 million for the Research Centers in Minority Institutions Programs within the Office of the Director. The Committee believes that the RCMI program is an effective mechanism to strengthen the research capabilities of minority institutions. The Committee is aware that NIH has begun exploring the concept of Institute co-funding of RCMI projects. The Committee believes that the additional interaction and support of the Institutes would hasten the development of the research infrastructure of these institutions and encourages NIH to implement co-funding. The Committee also urges NIH to reconsider its policy of not counting RCMI funds toward the Biomedical Research Support Grant eligibility, since the RCMI program now supports pilot projects. (Pages 86-87)	The FY 1990 appropriation for the RCMI program is $17.5 million, an increase of $2.2 million over the FY 1989 level. Co-funding with the other Institutes at the NIH is being explored by RCMI program staff; the NIAID is currently co-funding AIDS research at RCMI institutions at a level of $2 million. Because the purpose of the RCMI grants is to provide for the development of the research infrastructure of these institutions, rather than to support research, they are treated as other NIH core grants and center grants in the consideration for BRSG funds.
2. Director's Discretionary Fund The Committee has not approved the Budget request for a contingency reserve of $25 million. The Committee believes there are clear requirements for these funds throughout the NIH and has therefore distributed these funds based on its perception of scientific opportunity. (Page 87)	The NIH believes that the Director's Discretionary Fund is an important mechanism that would allow the NIH to respond more effectively to unforeseen changes in research direction and emerging research opportunities. Therefore, the FY 1991 request includes $20 million for this item.

Item	Action Taken or To Be Taken
3 NIH Supercomputer The Committee recognizes that the current capacity of the supercomputer at the National Institutes of Health needs upgrading in order to expand the ability to undertake state-of-the-art biomedical research. . . The Committee recognizes that the supercomputer is shared by other NIH institutes, the Department of HHS, and extramural scientists who are performing research appropriate for use of the supercomputer, and expects that to continue. The upgraded supercomputer will replace the present, overloaded supercomputer at NCI's Frederick facility in order to expand its capability and continue its work. The Committee intends that this purchase be completed during fiscal year 1990. This should be done using the normal competitive processes focusing on quality, capacity, appropriateness to current and future usage, and price. (Page 87)	In FY 1990, the National Cancer Institute will purchase a state-of-the-art high-speed, multi-processor, large-memory supercomputer with on-site support and maintenance. This upgrade will include major innovative computational resources, such as massively parallel architectures and special purpose processors. The new, upgraded facility will be available to users in FY 1991.
4 Diagnostic Radiology The Committee is concerned that there is no focus for intramural research in diagnostic radiology at NIH. During its hearings, the Committee learned of major advances in imaging technology which hold tremendous potential for the expansion of diagnostic radiology in clinical care. In order to capitalize on these promising areas of research, the Committee encourages the Director of NIH to establish an intramural research program for diagnostic radiology within an appropriate institute. (Page 87-88)	The Deputy Director for Intramural Research, NIH, is coordinating the development of a plan for a multi-institute Radiology Research and Training Program. The NIH has set aside $1.9 million in the FY 1990 OD appropriation to establish the program.

Office of the Director

Significant Items in Senate Appropriations Committee Report

Item	Action Taken or To Be Taken
1990 Senate Report	
1. Procurement Reforms	
The Committee is pleased to note the NIH is well along in the process of implementing numerous actions that will result in larger discounts on goods that NIH purchases from vendors . . . The Committee is reassured, . . . by NIH's commitment to achieve all possible savings while maintaining a system responsive to the needs of the scientists . . . The Committee also directs the NIH to continue to proceed at full speed in fully implementing procurement reform at NIH including efforts to streamline and professionalize NIH's procurement personnel. (Page 165)	The NIH has completed several major initiatives to improve its procurement of small purchases. For example, the NIH has obtained increased savings by individually negotiating new purchasing agreements with all of its high-volume vendors. This savings strategy has been augmented by consolidating procurements wherever feasible. Additionally, the NIH is reorganizing its procurement structure, which will reduce the number of staff who can place orders by 66 percent and the number of ordering offices by 36 percent. Also, as part of the reorganization, the use of full-time purchasing agents has been emphasized in order to build a more qualified professional purchasing staff.
2. Diagnostic Radiology	
The Committee agrees with a recent report of the Institute of Medicine asserting that the intramural program at NIH is a visible focus and rallying point for the Nation's overall biomedical research effort. (Page 165)	The Deputy Director for Intramural Research, NIH, is coordinating the development of a plan for a multi-institute Radiology Research and Training Program. The NIH has set aside $1.9 million in the FY 1990 OD appropriation to establish the program.
3. Research Centers at Minority Institutions	
The Committee recommends that each of the individual NIH Institutes aggressively pursue the initiation of institutional co-funding of	The FY 1990 appropriation for the RCMI program is $17.5 million, an increase of $2.2 million over the FY 1989 level.

Item	Action Taken or To Be Taken
research centers at minority institutions (RCMI) grants . . . The Committee recommends that each Institute support the RCMI program by sponsoring programs and research of interest to the Institute, matching the RCMI recipients' capabilities and expertise. (Page 167)	Cofunding with the other Institutes at the NIH is being explored by RCMI program staff; the NIAID is currently cofunding AIDS research at RCMI institutions at a level of $2 million.
4. Sleep Disorders	
. . . The Committee would appreciate being kept informed of various developments in this area, including the proposed role for the newly established National Commission on Sleep Disorders. (Page 167)	A report has been prepared for the Committee.

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1990 Amount Authorized	1990 Appropriation	1991 Amount Authorized	1991 Budget Estimate
Funded Authorizations:						
Office of the Director.....	Title IV, Section 402(b)	40 USC282	Indefinite	$89,916,000	Indefinite	$82,975,000
Total Budget Authority...				89,916,000		82,975,000

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National Institutes of Health

Office of the Director

Appropriations History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1982	$20,682,000	$36,502,000	$23,502,000	$23,618,000
1983	24,283,000	24,683,000	24,683,000	24,683,000
1984	26,720,000	26,779,000	26,720,000	26,720,000
1985	27,509,000	47,509,000	38,304,000	37,082,000 2/
1986	37,085,000	117,085,000	37,574,000	133,189,000 3/
1986 Sequester				-5,031,000
1987	36,701,000	246,651,000	56,708,000	57,463,000 4/5/
1988	59,819,000	71,389,000 6/	61,284,000	61,819,000
1989	59,578,000	71,578,000	65,578,000	72,201,000
1990	96,570,000	106,987,000	127,570,000	108,468,000 7/
1990 Sequester				-1,049,000
1991	82,975,000 8/			

1/ Reflects enacted supplementals, rescissions, and reappropriations.
2/ Includes $10,000,000 for the initiation of a program that supports biomedical research in small and minority schools and universities.
3/ Includes $20,000,000 for the continuation of a program that supports biomedical research in small and minority schools and universities, and $70,000,000 for research on AIDS. Includes $16,197,000 transfer from HRSA for establishment of the National Center for Nursing Research.
4/ Includes a transfer of $755,000 to cover the FERS increase and partial costs of the pay raise.
5/ The Budget Estimate to Congress proposed that all funding for AIDS research be consolidated in the Office of the Assistant Secretary for Health. The House Allowance consolidated all NIH AIDS funding in the Office of the Director, NIH; the Senate Allowance and the Appropriation spread the funding among the Institutes.
6/ Does not include funding for AIDS research. Consolidated at the Secretary's level.
7/ Excludes enacted administrative reduction of $519,000.
8/ The 1990 appropriation and 1991 estimate excludes $200,000 in permanent budget authority expected to be realized from Cooperative Research and Development Agreements.

Justification

Office of the Director

	1990 Appropriation		1991 Estimate		Increase or Decrease	
	FTEs	BA	FTEs	BA	FTEs	BA
TOTAL	601	$89,916,000	612	$82,975,000	+11	-$6,941,000
HIV/AIDS	(35)	(10,551,000)	(37)	(13,747,000)	(+2)	(+3,196,000)

General Statement

The appropriation for the Office of the Director (OD) of the National Institutes of Health provides funds for the central administration and services to the NIH Institutes, Centers and Divisions. While each major component of the NIH administers the activities associated with its specific programs, the Office of the Director is responsible for their overall direction and coordination. The major units within the OD are headed by NIH Associate Directors responsible for central areas such as extramural and intramural research policy and the coordination of scientific inquiry; coordination of NIH AIDS research and establishment of NIH-wide AIDS-related policies and operations; coordination and direction of minority research and training programs; analysis of legislation, program planning and evaluation and leadership in recombinant DNA activities; coordination of public affairs and other communication activities; contract and grant administration, investigation and review, financial management, management policy and personnel operations; and promotion of disease prevention, nutrition research and medical applications of research. A number of other offices are responsible for NIH-wide direction and centralized services in such areas as equal opportunity and the promulgation of policies and procedures related to prevention and investigation of misconduct in science.

Overall Budget Policy

The FY 1991 total budget request for the Office of the Director is $82,975,000. This represents a decrease of $6,941,000 from the comparable FY 1990 budget authority of $89,916,000. This request includes $11,372,000 for the Academic Research Enhancement Award (AREA) Program, $2,065,000 for the Intramural Radiology Program, $20,000,000 for an NIH Director's Discretionary Fund and $13,747,000 for the AIDS Research Program. The request for the Research Centers for Minority Institutions (RCMI) Program, which was previously included in the OD appropriation, is included in the Division of Research Resources appropriation.

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Program Accomplishments

Because scientific inquiry frequently extends across organizational lines, many research and research-related administrative activities involve two or more Institutes, Centers or Divisions. The Office of the Director coordinates trans-NIH activities, provides leadership for NIH-wide initiatives and, in addition, operates common services for all NIH components. Examples of such efforts in which the OD plays a central role include the following.

The Office of Intramural Research was recently reorganized to reflect the establishment of the Office of Technology Transfer (OTT). Formerly known as the Office of Invention Development, this office is the primary focus for implementation and information exchange on invention reporting, patent application and licensing, and training of NIH scientist in technology management matters. Through the OTT, the NIH and Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) have taken the leadership role within the Department to implement the Federal Technology Transfer Act of 1986. Total patent royalty collections in FY 1989 were approximately $4.8 million. In addition, by the end of FY 1989, over 100 Cooperative Research and Development Agreements (CRADAs) had been entered into with private companies, and numerous others were under negotiation.

The Office of Scientific Integrity (OSI) was established within the NIH in March 1989 to serve as a focal point within the PHS for overseeing the implementation of policies and procedures designed to safeguard the integrity of research conducted and supported by PHS agencies.

The OSI has assumed responsibility for all active and ongoing cases of possible scientific misconduct on file at the NIH and ADAMHA. These cases constitute a large majority of those within the PHS. A comprehensive data base of all OSI cases has been planned and will be shortly implemented.

The OSI was a major participant in the revision and publication of the "Final Rule on Responsibilities of Awardee and Applicant Institutions for Dealing With and Reporting Possible Misconduct in Science." This rule outlines the responsibilities of extramural research institutions for establishing and implementing administrative policies and procedures for reviewing and reporting allegations of misconduct in science supported by the PHS. The rule also describes the new requirement for applicant and awardee institutions to have on file with the OSI an assurance that they have policies and procedures in place to meet the requirements of the Final Rule and will abide by their own policies and procedures.

The OSI has moved rapidly to strengthen and, where necessary, create cooperative working relationships with key individuals and offices within the PHS, as well as other agencies throughout the federal research community, including the DHHS Office of the Inspector General, the Department of Veterans Affairs, the Department of Agriculture, the Environmental Protection Agency and the National Science Foundation.

In response to expressions of public concern regarding potential conflicts of interest in NIH-sponsored biomedical research projects, the NIH and ADAMHA held an open meeting on June 27-28, 1989. Information presented and discussed at that meeting with representatives from the academic,

government, and industrial sectors served as background for the drafting of a Request for Comment on Proposed Guidelines for Policies on Conflict of Interest published September 15, 1989, in the NIH Guide for Grants and Contracts. Over 740 comments were received and will serve as the basis for identifying appropriate options for next steps, as directed by Secretary Sullivan.

The Office for Minority Programs (OMP) is being established in the OD to develop NIH-wide goals for minority research and training programs and to coordinate the direction of these programs. The OMP will be under the supervision of the Associate Director for Minority Programs. Functions of the OMP will include development and coordination of a trans-NIH plan for minority research and training in minority and non-minority institutions; implementation of a plan to enable the NIH to improve the effectiveness of all programs aimed at increasing minority participation in biomedical research; and coordination of NIH policy on minority health issues. The Associate Director position was advertised nationally and the interview process has been completed. It is expected that the position will be filled early in 1990.

The NIH and ADAMHA convened representatives of the six Public Health Service agencies to develop a strategy and action plan addressing animal research and welfare issues. The primary goal of the action plan is to foster leadership in educating the general public, policymakers and legislators, the research community, educators, and professional and voluntary health organizations on the continuing need to use animals in the conduct of health research and product safety testing. The Working Group prepared a draft document addressing these issues, which was subsequently approved by agency heads and submitted to the Assistant Secretary for Health on January 4, 1989. The Group anticipates refining and expanding upon the proposed actions, assigning priorities, and setting deadlines for completing the initiatives.

The Office of Science Policy and Legislation (OSPL) initiated programs to foster biomedical science literacy and interest in science education. The OSPL provided information about training opportunities in biomedical and health research to multiple audiences, including a symposium on biomedical research and career opportunities for American Indian and Alaska Native students and their educators in collaboration with the Indian Health Service (IHS). A second joint NIH/IHS national symposium is planned for the summer of 1990. The OSPL also implemented a career opportunity program for Hispanic Americans. The OSPL is collaborating with representatives of the pharmaceutical industry in the development of a middle-school pilot curriculum supplement on biomedical careers for use in New Jersey in 1990.

The NIH continued to implement its procurement action plan in order to achieve a balanced purchasing system that is, in addition to being responsive, one that is economical and consistent with procurement regulation. Notable accomplishments during FY 1989 included:

- The Division of Procurement completed negotiations with 65 high-volume vendors whose Blanket Purchase Agreements account for $39 million annually in sales to the NIH. These actions should result in significant savings in FY 1990.

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- A system of oversight was established which will provide strict oversight of purchases made through our Delegated Procurement System. A program of daily scanning of purchases augmented by on-site reviews has been established. These reviews should result in improved regulatory compliance in the various ordering offices.

- Criteria were developed to provide for the centralization of procurement in the Institutes and Divisions. As a result, the number of ordering officials will be reduced by two-thirds, the number of approving officials by 43 percent and the number of ordering offices by 36 percent.

The NIH is making a special effort through the Academic Research Enhancement Award (AREA) Program to stimulate research in educational institutions that provide baccalaureate training for a significant number of our nation's research scientists but historically have not been major recipients of NIH support. The AREA Program, administered by the Office of Extramural Research (OER), is designed to support new research projects or expand ongoing research activities in areas related to the health sciences at such eligible institutions. In FY 1989 119 awards were made totaling approximately $11 million. A workshop will be held in FY 1990 to assess the goals, impact and future directions of the AREA Program. Participants will include faculty members and other representatives of AREA applicant institutions.

In cooperation with nine other Federal agencies, the NIH broadened to 50 institutions the participation in the Federal Demonstration Project whose goal is to simplify and streamline administrative procedures and thus to enhance research productivity. Two pilot projects were initiated to minimize the effort required in the noncompeting grant funding process and to simplify and improve compliance with administrative certifications and assurances by utilizing a master checklist.

The Division of Equal Opportunity (DEO) recruited, selected, and trained 25 new NIH EEO Counselors to provide a full complement of counselors available to NIH employees and applicants. The DEO also trained 10 counselors in mediation and negotiation techniques. A Black Employment Program was established and a program manager was hired to strengthen recruitment and employment of blacks in scientific and administrative positions.

During FY 1989, the OD provided administrative and staff support for two meetings of the Recombinant DNA Advisory Committee (RAC) and six meetings of its subcommittees. A proposal for human gene transfer submitted by NIH intramural researchers was approved by the RAC and the Director, NIH. A pamphlet explaining both the scientific basis and the ethical considerations of human gene therapy in language geared toward the general public is in preparation for publication and broad distribution early in 1990.

The Office of Extramural Research published and implemented four new or expanded initiatives for support of underrepresented minorities in biomedical research including mechanisms to support undergraduate and graduate students and faculty members and expansion of the Minority High School Research Apprenticeship Program. OER staff also conducted five regional hearings to determine how the NIH programs could more efficiently increase participation of minorities in biomedical science.

The Division of Personnel Management continued its lead role in implementing the special pay flexibilities and other benefits authorized under U.S.C. Title 38. In July 2, 1986, the President signed P.L. 99-349 which provided to NIH Clinical Center nurses the same pay and schedule options and benefits available to nurses employed by the Department of Veterans Affairs. On September 20, 1988, the President signed the DHHS Appropriations Bill which included a provision that expanded the special pay flexibilities and other benefits of Title 38 to all nurses and allied health specialists at the NIH. The flexibilities implemented under Title 38 have significantly improved the NIH's ability to recruit and retain staff in critical clinical health occupations. The NIH plans to utilize other significant features of Title 38 including recruitment/retention bonuses and direct hire authority to further enhance our ability to keep these occupations staffed at peak operating levels.

The Office of Communications Radio News Service has achieved excellent results with a series of one-minute medical research reports available via an 800 number to all radio stations in the U.S. The service features one story per week, but breaking stories are inserted as they happen. The stories deal with current research advances and scientific information often tied to seasonal ailments or special events. The service currently reaches 270 to 350 radio stations per week with an estimated weekly total of two million listeners.

The Office of Disease Prevention (ODP) conducted five consensus development conferences in FY 1989. Through these conferences, the safety and effectiveness of emerging and established technologies are assessed and discussed in a public forum. Topics of recent conferences included Oral Complications of Cancer Therapies; Sunlight, Ultraviolet Radiation, and the Skin; and Treatment of Destructive Behaviors in Persons with Developmental Disabilities. The ODP also convened a three-day conference entitled "Modeling in Biomedical Research: An Assessment of Current and Potential Approaches" to survey the variety of model systems available in biomedical research and to determine their applicability as alternative animal models. The Division of Nutrition Research Coordination hosted and organized the Interagency Committee on Human Nutrition Research's Fourth Conference on Federal-Supported Human Nutrition Research Units and Centers in February 1989. The Division of Disease Prevention held six disease prevention conferences, including "Genes Involved in the Pathogenesis of Lung Cancer", "Childhood: Its Role in Adult Obesity"; and "Strategies for Lyme Disease Prevention and Control".

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AIDS Research Program

OD AIDS Program

The NIH Director established the Office of AIDS Research (OAR) in 1988 to serve as the focal point for AIDS research conducted and funded by the various Institutes, Centers and Divisions. Specifically, the purpose of the office is to coordinate NIH intramural and extramural AIDS research; centralize various AIDS-related policy and operating functions; and represent the Director, NIH, on AIDS-related matters. An additional major function of the office is the development and coordination of the NIH budget request for AIDS.

The Intramural AIDS Targeted Antiviral Program was established in the Office of the Director to support basic research on the structure and function of the human immunodeficiency virus (HIV). The goal of the program has been to utilize the methods of structural biology, molecular biology, and biochemistry to develop new leads for agents that can be used in the treatment of AIDS. The general approach is to seek information from these basic studies that will facilitate design of new drugs that interfere with the virus life cycle by blocking the function of the HIV proteins or nucleic acids. Understanding how HIV proteins and nucleic acids function should also contribute to the therapy problem through the development of new methods for drug screening and by the identification of new molecular targets for antiviral agents.

Recent Research Accomplishments

The OAR staff recruitment has been completed with representation in various functional areas that manage the activities of the office, such as program analysis, medical and basic science activities. In order to make efficient use of scarce resources, administrative support for budget and legislative services are provided through existing NIH offices. Activities performed by this office included the following:

- Coordinated the development of an NIH plan for the medical management of NIH employees occupationally exposed to HIV. This effort has evolved into an activity of the Center for Disease Control to develop PHS recommendations in this area which closely parallels the NIH practice.

- Coordinated the establishment of a cohesive plan to double the capacity of the outpatient AIDS programs of the NCI and the NIAID in accordance with the Health Omnibus Program Extension Act (P.L. 100-607).

- Initiated collaborative efforts under the AIDS section added to the U.S.-U.S.S.R. Agreement on Cooperation in the Field of Medical Science and Public Health in November 1988, resulting in the exchange in both directions of scientists for the purpose of defining collaborative AIDS research projects. The first visit of Soviet scientists under this agreement has taken place and in turn plans are being finalized for a visit of U.S. scientists to the U.S.S.R.

- Conducted the third and fourth meetings of the AIDS Program Advisory Committee (APAC), which advises the Director, NIH, on overall AIDS-related research directions, scientific opportunities and major program initiatives to be undertaken by the NIH. The committee addressed the issues of AIDS therapeutics, pediatric HIV infection, and access to clinical trials for underserved populations. Other PHS agencies involved in clinical care issues--the Food and Drug Administration, the Health Resources and Services Administration, and the Health Care Financing Administration--met with the Committee to discuss cooperative efforts with NIH in the expansion of clinical trials to reach minorities, women and children. This meeting resulted in a collaborative effort between HRSA and NIAID to provide health care delivery services to the NIAID Pediatric Clinical Trial Units. This accomplishment was applauded by the National AIDS Program Office (NAPO).

- Developed and pursued the goal of increased access to treatments for HIV infected individuals, resulting in the expansion of the "Treatment IND" (Investigational New Drug) mechanism. Under this mechanism, the FDA allows a drug to be marketed only for a specific purpose. The drug is still experimental and is not licensed for any purpose other than for specific treatment of a specific illness. This has evolved into an enlarged nationwide program of earlier access to experimental, state-of-the-art treatments for those individuals who are unable to participate in clinical trials. This is an effort that has received cooperation from the FDA and many public interest groups.

- At direction of the NIH Director, began the design of a centralized AIDS Research Information System (ARIS). This agency-wide system to track and categorize the funding of AIDS research will enable NIH staff to respond to inquiries from Congress, the public and Federal officials concerning expenditure of funds, FTE support and information regarding grants for NIH research programs. While there are grant tracking mechanisms in place, as well as Institute-specific data collection, the ARIS will be the first NIH-wide system to capture all of this data.

- Coordinated implementation of a single, centralized information system for AIDS clinical trials. Information about NIH-sponsored trials is provided by the NIAID; information about the privately sponsored trials is provided by the FDA. This activity is coordinated and directed by the NLM as the AIDSTRIALS database, which makes this information available electronically all over the world. Current information is now available to health care professionals as well as participants by calling a nationwide toll-free telephone number.

- The Director of the OAR, in reviewing the continuing budgetary and programmatic growth of the NIH AIDS Research program, assessed the need for an independent outside program evaluation, including but not limited to, an evaluation of the appropriateness of the research priorities, appropriateness of the dollar allocation among the various research categories and the adequacy of the level of funding for extramural and intramural research. After consultation with a group of external scientific experts, a detailed contract for such a review was developed. The National Academy of Sciences/Institute of Medicine has begun their evaluation with an anticipated final report due in November 1990.

- Initiated implementation and management of the NIH AIDS Loan Repayment Program. Public Law 100-607 authorizes a program for repayment of a sizeable portion of the accumulated educational loan debt of health professionals who agree to conduct, as NIH employees, research with respect to AIDS.

Many of the very best scientists at the NIH have been attracted by the Intramural AIDS Targeted Antiviral Program to work on AIDS for the first time. At present, 41 separate research groups from ten different institutes are being supported by the program. Structural biology projects include the determination of the three-dimensional structure of HIV proteins in both crystal and solution by state-of-the-art X-ray and nuclear magnetic resonance methods. Biochemical studies include elucidation of the molecular mechanism of the viral enzymes--reverse transcriptase, ribonuclease H, and the protease. All three enzymes are unique to the virus and are therefore excellent targets for drugs. Molecular biology studies are concerned with the mechanism of integration of the viral DNA into the host DNA, the mechanism of activation of the provirus and the control of expression of the viral DNA, and the cellular processing and modification of the viral polypeptides to form the functioning viral components.

Many of the projects require highly purified HIV proteins. To meet this need a central facility has been established during the past year to produce such proteins in sufficient purity and quantity for structural, physio-chemical, and pharmacological studies, and two experts in this area have been recruited from the biotechnology industry. The laboratory is now being established in the new Building 6B and will be ready for operation in the spring of 1990.

Over the past year there have been a number of major new findings that have resulted from the research supported by the Program. These include:

- Determination of the complete three-dimensional structure of interlukin-8 in solution by nuclear magnetic resonance. This is a key protein in the response of the immune system to HIV infection.

- Development of a new therapeutic agent. This agent, which contains a powerful bacterial toxin, selectively kills T-cells that contain a replicating virus and prevents the spread of HIV infection in cell cultures. It is now being developed further for possible clinical trials.

- Discovery that a commonly used drug, dipyridamole (DPM), increases the antiviral effect of AZT while reducing its toxicity. A clinical trial using combination AZT/DPM therapy is being planned.

Research Plans

The OAR will continue to serve as the focal point for AIDS research within the Office of the Director. The office plays a key role in developing and operating the management process needed for coordination of the NIH AIDS research program.

The OAR, in conjunction with the Division of Safety, will initiate the publication of the NIH HIV Safety Alert. This will serve as a mechanism to

provide employees in laboratory and clinical research areas with up-to-date AIDS safety information.

The sharing of information about advances in AIDS research has proven to be a formidable task, as witnessed at the Annual International AIDS conferences. In 1990, the OAR will initiate a series of AIDS technology transfer meetings to enhance the sharing of information on safety, AIDS technology, and AIDS related research at regional meetings throughout the U.S. The NIH plans to hold three or four meetings in 1990 and plans to expand the program to six meetings in 1991.

The request for the OD includes funds to finance the second cohort of program participants in the AIDS Research Loan Repayment Program, as well as funds to cover related administrative costs. While it is anticipated that 150 to 200 applications for participation in this program will be filed in FY 1990, a dramatic increase in FY 1991 is expected due to program announcements, better understanding of the program by Institute personnel offices and increased peer referrals. The OAR negotiated an agreement in 1990 with HRSA to administer the program.

It is anticipated that ARIS, the on-line AIDS information database, will be ready for implementation in the Institutes and Divisions during FY 1991. The request provides additional funds to support this implementation and to provide training and technical support for the system.

The OD will continue to fund the Intramural Targeted Antiviral Program. The request provides resources to expand the program. Funding for seven new investigations was authorized in FY 1990. In order to promote continuity to the program, projects are generally approved on a two-year basis. All projects currently funded will be due for renewal during FY 1991. It is expected that approximately 80 to 85 percent of these are likely to merit continued funding at approximately the same dollar level. It is also expected that at least another 25 to 30 new proposals will be submitted for review. Between one quarter and one third of these proposals will probably be highly rated by the review panel and recommended for funding.

It is vital for the program to obtain the three-dimensional structures for the important proteins encoded by the HIV virus so that a rational plan for the development of agents which inhibit these proteins can be constructed. This requires, first of all, the isolation of these proteins in a pure form. Accordingly, a Protein Expression Laboratory has been established and is being staffed. A workshop will be held in January 1990 to determine exactly which proteins should be produced first. After this, the proteins will be produced either in bacteria or in cell culture. When large amounts are obtained and purified, they will be crystallized and examined, either by X-ray diffraction or nuclear magnetic resonance, so that their three-dimensional structure can be determined. Finally, the structures will be submitted to medicinal chemists and pharmacologists for the development of drugs that may inhibit the important enzymes necessary for HIV's infectivity and reproduction.

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Office of the Director

Research Management and Support

Authorization: Indefinite

Budget Authority:

1990 Appropriation		1991 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA
601	$89,916,000	612	$82,975,000	+11	-$6,941,000

Purpose and Method of Operation

The Office of the Director provides leadership, focus and direction to the NIH research community, and coordinates and directs initiatives which cut across the Institutes and Divisions of NIH. The OD is responsible for the development and management of intramural and extramural research and research training policy, the review of program quality and effectiveness, the coordination of selected NIH-wide program activities, and the administration of centralized support activities essential to operations of the NIH.

Several offices in the OD provide policy and direction to the NIH research community:

The Office of Extramural Research provides guidance in the development and management of extramural (grant, cooperative agreement and contract) research and training programs and oversees the protection of human subjects and the proper care and use of laboratory animals on behalf of the entire U.S. Public Health Service.

The Office of Intramural Research implements and coordinates intramural research policy and programs, provides staff support to the NIH Scientific Directors, represents the intramural programs on task groups and ad hoc committees and provides overall direction to the intramural research program.

The Office of Science Policy and Legislation provides leadership and guidance to NIH programs concerning science policy, program planning, program evaluation, health economics and the development and implementation of health legislation. The Office also provides staff direction and support to the Advisory Committee to the Director, NIH, and the Recombinant DNA Advisory Committee.

The Office of AIDS Research, which broadly coordinates the NIH intramural and extramural AIDS research effort, is a centralized locus for various AIDS-related policy and operating functions and represents the Director, NIH, on AIDS-related matters.

Through the Office of Disease Prevention, the OD coordinates activities concerning research related to disease prevention and promotion of disease prevention research; all aspects of nutrition research relating to the mission of NIH; and medical applications of research including drugs, procedures, devices, and other technology developed from basic biomedical research at NIH.

There are also a number of administrative and managerial support functions in the Office of the Director:

The Office of Communications plans and directs activities designed to achieve better understanding of NIH programs and accomplishments on the part of the general public, Congress, biomedical institutions and the medical profession. This office also coordinates the public affairs and other communication activities of the Institute and Division offices concerned with communications, public affairs and scientific reports.

The Division of Equal Opportunity is responsible for providing policy direction, planning and monitoring of the Equal Opportunity Program. The office develops the NIH Affirmative Action Program and monitors its implementation in cooperation with NIH components and is also responsible for the administrative processing of complaints of discrimination, including resolving informal disputes.

The Office of Administration is the component of the OD responsible for providing leadership and guidance in all phases of management. This office provides central services to all of the NIH in the areas of budget and financial management, personnel management, management policy, grant and contract management and administration, and management surveys and reviews.

Rationale for the Budget Request

The 1991 budget request of $82,975,000 for the research and management support activity of the Office of the Director (OD) includes $11,372,000 for the Academic Research Enhancement Award (AREA) Program, which represents an increase of $363,000. This program provides important support to biomedical research programs at non-research-intensive educational institutions, primarily, four-year undergraduate colleges. The 1991 request provides $35,791,000 for funding of the central administrative offices that comprise the OD. This represents an increase of $2,895,000 over the 1990 level.

The request also includes $20 million for an NIH Director's Discretionary Fund. This fund, which will be allocated to the individual components and mechanisms of the NIH at a later time as the need arises, will allow NIH to be more responsive to new issues, emergencies, or research opportunities of high priority.

Numerous issues in biomedical research and the health sciences will continue to require the attention of the offices and divisions within the OD. These include the following initiatives:

The Office of Scientific Integrity (OSI) was established in the OD in 1989. In 1991, the Office will operate with a staff of 15 employees and a budget of approximately $1,408,000. The OSI will continue to carry the lead responsibility for completing the revision of the existing PHS policies and

procedures for handling cases of possible scientific misconduct, including procedures for extramural, intramural and regulated research.

The OSI will also initiate education and prevention activities, including, e.g., a workshop of journal editors to discuss the response of the scientific literacy community when problems of alleged or confirmed scientific misconduct are revealed and a workshop of institutional officials and attorneys to discuss the growing importance of legal issues in the conduct of inquiries and investigations of possible scientific misconduct.

A key objective for the OSI is to monitor carefully implementation of the "Final Rule on Responsibilities of Awardee and Applicant Institution for Dealing With and Reporting Possible Misconduct in Science." In this regard, the Office will work actively with institutions as they begin to implement their procedures and will consult with them as appropriate as they deal with complexities of implementation. The OSI will review a random sample of institutions' policies and procedures for conformance to the requirements of the rule.

The Office for Protection from Research Risks (OPRR) in the Office of Extramural Research will continue to conduct regional workshops for administrators and investigators at awardee institutions to foster greater understanding and compliance with the PHS Animal Welfare Policy and to identify the essentials for operating effective and responsive animal care programs. The OPRR will continue to represent the PHS in working with the USDA to develop regulations covering such issues as proposed standards for psychological well-being of primates; exercise for dogs; and humane handling, care, and treatment of other research animals. These regulations are in response to the 1985 Amendments to the Animal Welfare Act, which directed the USDA to promulgate additional regulations governing the care and use of animals in biomedical research.

The OD is the focal point for NIH activities in the area of biomedical science education and for leading the PHS Biomedical Education Initiative. Specific activities will include: (1) developing the initial PHS Biomedical Science Education Action Plan, including goals and actions, and overseeing the implementation of the plan, once approved; (2) developing an NIH action plan that will focus on scientific literacy and the next generation of biomedical scientists and support personnel; (3) planning and conducting a national symposium on training and career opportunities in the biomedical sciences for American Indians and Alaskan Natives; (4) working with the Association of Minority Health Professions Schools to sponsor a national symposium on training and career opportunities in the biomedical sciences for Black Americans; and (5) working with the new NIH Associate Director for Minority Programs to build on previous activities initiated by the office to attract minority students to biomedical science careers.

The OD Local Area Network (OD LAN) provides computer network services that link the central administrative offices of the OD, improves communications and provides for document transferral. Facilities available on the OD LAN include electronic mail, network applications (e.g., shared word processing), pooled communications, and shared resources (e.g., shared files and shared printers.) The OD LAN became operational in 1989 and is currently supporting over 100 active users. The current plans for the OD LAN call for over 400 active users by the end of FY 1991.

The Office of Administration will continue implementation of the NIH action plan to improve its station support acquisition activities. The FY 1991 NIH budget assumes a savings of $3.2 million, in addition to the savings generated in FY 1989/1990 from the various cost savings measures that will continue to be taken.

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NATIONAL INSTITUTES OF HEALTH

Office of the Director

Detail of Permanent Positions

	1989 Actual	1990 Estimate	1991 Estimate
ES-5	2	2	2
ES-4	13	17	17
ES-3	1	1	1
ES-2	0	0	0
Subtotal	16	20	20
GS/GM-15	32	35	35
GS/GM-14	51	56	59
GS/GM-13	90	98	101
GS-12	68	77	79
GS-11	34	40	41
GS-10	6	6	6
GS-09	36	46	46
GS-08	11	11	11
GS-07	59	67	68
GS-06	37	40	40
GS-05	32	36	37
GS-04	16	18	18
GS-03	7	7	7
GS-02	7	7	7
GS-01	0	0	0
Subtotal	486	544	555
Grades established by the act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General Grade	1	1	14
Director Grade	10	10	10
Senior Grade	3	3	3
Full Grade	2	2	2
Junior Assistant	2	2	2
Subtotal	18	18	18
Total Permanent Positions	520	582	593

NATIONAL INSTITUTES OF HEALTH

Office of the Director

New Positions Requested

	Grade	1991 Number	1991 Annual Salary
Research Management and Support			
Medical Officer	GS-14	2	$117,098
Health Science Administrator	GS-14	1	58,549
Health Science Administrator	GS-13	2	99,092
Program Analyst	GS-13	1	49,546
Program Analyst	GS-12	2	83,329
Program Analyst	GS-11	1	34,763
Secretary (Typing)	GS- 7	1	24,177
Clerk Typist	GS- 5	1	20,640

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NATIONAL INSTITUTES OF HEALTH

Office of the Director

Advisory and Assistance Services

For FY 1991, the Advisory and Assistance Services budget will be $4,770,000, an increase of $148,000 over FY 1990. These funds will continue to support the NIH Program Evaluation Fund and the Acquired Immunodeficiency Syndrome Program Advisory Committee.

The Office of the Director, NIH, is responsible for the NIH program evaluation funds which are authorized by Section 513 of the Public Health Service Act. Program evaluation funds are to be used at the discretion of the Secretary, HHS, for the evaluation of health programs. These evaluation studies aim to assist in program development and management decision making. The budgeted amount includes the NIH Program Evaluation funds which are totally reimbursed from the NIH BIDs. The estimate does not include the funds for the Office of the Assistant Secretary for Health or the Office of the Secretary.

The Office of the Director supports the Acquired Immunodeficiency Syndrome Program Advisory Committee. Consultant services requirements are necessary for the compensation of non-federal committee members. This committee is authorized by law and chartered by the Secretary, HHS. The advisory committee provides knowledgeable advice, suggestions, and criticisms of ongoing and proposed NIH AIDS research activities to the Secretary, HHS, the Assistant Secretary for Health and the Director, NIH.

All requisitions charged against the NIH Program Evaluation Fund must be reviewed and approved by the Planning and Policy Research Branch. All consultant services obligations are reviewed and reconciled against the approved consultant services ceiling and the quarterly report issued by the Operations Accounting Branch, DFM.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Acquired Immunodeficiency Syndrome

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NATIONAL INSTITUTES OF HEALTH

FY 1991 AIDS PRESIDENT'S BUDGET
(Dollars in thousands)

	FY 1989 Budget Authority	FY 1990 Approp.	FY 1990 Estimate
NCI	$124,148	$150,304	$160,807
NHLBI	38,611	42,056	44,463
NIDR	4,141	4,662	5,002
NIDDK	3,676	5,320	5,791
NINDS	13,432	16,158	17,227
NIAID	312,888	393,958	423,407
NIGMS	10,901	14,614	15,487
NICHD	22,704	26,749	29,010
NEI	4,965	5,533	5,887
NIEHS	4,197	4,291	4,580
NIA	502	859	929
NIAMS	733	1,238	1,483
NIDCD	---	---	578
DRR	45,210	46,096	48,379
NCNR	761	987	1,148
FIC	4,654	4,898	5,207
NLM	79	493	532
OD	5,792	10,551	13,747
B&F	4,900	14,765	16,500
TOTAL	602,294	743,532	800,164

NATIONAL INSTITUTES OF HEALTH

AIDS
FY 1991 President's Budget

(Dollars in thousands)

Mechanism	FY 1989 Bud. Auth. No.	FY 1989 Bud. Auth. Amount	FY 1990 Appropriation No.	FY 1990 Appropriation Amount	FY 1991 Estimate No.	FY 1991 Estimate Amount
Research Grants:						
Research Proj.:						
Noncompeting	391	$173,322	495	$223,269	613	$269,451
Admin. Suppl.	(10)	600	(2)	57	(2)	59
Competing	255	56,843	239	66,278	239	46,568
Subtotal	646	230,765	734	289,604	852	316,078
Research Centers:						
Spec/Comp	11	15,245	12	15,443	12	15,589
GCRC		17,672		22,633		23,431
Biotechnology		342		368		381
LASPR	11	15,757	11	17,258	11	17,868
RCMI		3,329		3,372		4,072
Subtotal	22	52,345	23	59,074	23	61,341
Other Research:						
Careers	15	952	17	1,168	16	1,086
Clin. Ed						
Coop. Cl	3	3,450	3	3,797	3	3,837
BRS		1,682		765		792
MBRS		234		190		260
Other Rel. Res.	36	8,877	32	7,651	31	7,850
Subtotal	54	15,195	52	13,571	50	13,827
Total RGs	722	298,305	809	362,249	925	391,246
Research Training:						
Individual	72	1,766	72	1,933	72	1,965
Institutional	224	4,767	233	5,384	233	5,538
Total, Trng	296	6,533	305	7,317	305	7,503
R&D Contracts	247	166,743	285	198,637	292	207,994
Intramural Research		93,388		122,458		134,892
Res. Man. & Supp.		21,614		26,187		27,750
Control						
Construction		4,940		875		
TOTAL, BID'S		591,523		717,723		769,385
Nat. Lib. of Med.		79		493		532
Office of Director		5,792		10,551		13,747
Buildings and Fac.		4,900		14,765		16,500
		602,294		743,532		800,164

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NATIONAL INSTITUTES OF HEALTH

AIDS FUNDING BY FUNCTIONAL CATEGORY

(Dollars in thousands)

Category	FY 1989 Bud. Auth.	FY 1990 Appropriation	FY 1991 Estimate
I. BASIC SCIENCE RESEARCH:			
A. Biomedical Research:			
1. HIV and HIV genome	$62,120	$66,320	$71,887
2. Immunology	37,954	44,911	48,075
3. Blood/Blood products	11,063	12,154	8,879
4. Diagnostic methods/reagents develop	7,869	10,853	11,959
5. Animal models and related studies	29,683	36,308	39,264
SUBTOTAL, Biomedical Research	148,689	170,546	180,061
B. Neuroscience and Neuropsychiatric Research	16,645	20,324	21,969
C. Behavioral Research:			
1. Mechanisms of behavior and behavior change	3,863	4,188	4,730
2. Prevention of high-risk behaviors	1,315	611	642
SUBTOTAL, Behavioral Research	5,178	4,799	5,372
D. Therapeutic Agents:			
1. Development	131,421	163,712	176,082
2. Clinical Trials	103,840	139,966	150,306
SUBTOTAL, Therapeutic Agents	235,261	303,678	326,388
E. Vaccines:			
1. Development	49,238	64,301	70,499
2. Clinical Trials	10,581	14,332	15,631
SUBTOTAL, Vaccines	59,819	78,633	86,130
F. Research Enhancement:			
1. Training	6,473	8,253	9,445
2. Construction (Extramural)	4,940	---	---
SUBTOTAL, Research Enhancement	11,413	8,253	9,445
TOTAL, BASIC SCIENCE RESEARCH	477,005	586,233	628,865

Category	FY 1989 Bud. Auth.	FY 1990 Appropriation	FY 1991 Estimate
II. RISK ASSESSMENT AND PREVENTION:			
A. Surveillance:			
1. Diseases associated with HIV	7,206	8,263	8,981
SUBTOTAL, Surveillance	7,206	8,263	8,981
B. Population-Based Research: Natural History, Transmission, Risk Factors:			
1. Transmission:			
a. Sexual	33,201	37,353	43,290
b. Intravenous drug abusers	8,583	10,683	11,460
c. Hemophilia populations	4,692	4,676	4,856
d. Blood recipient/donor studies	9,420	9,400	8,839
e. Perinatal infection	18,480	23,341	25,254
f. Occupationally related	83	83	100
g. Other/Miscellaneous	13,560	16,245	17,284
SUBTOTAL, Transmission	88,019	101,781	111,083
2. Natural history and cofactors	12,717	16,154	16,951
SUBTOTAL, Population based research	100,736	117,935	128,034
C. Information and Education/Preventive Services:			
1. High risk or infected persons:			
a. Health education/risk education	2,057	1,797	1,826
b. Counseling, testing, partner notification	275	344	369
c. Perinatal AIDS prevention projects	447	560	601
SUBTOTAL, High-Risk or Infected Persons	2,779	2,701	2,796
3. School and college aged youth:			
a. National efforts	533	668	716
SUBTOTAL, School and college aged youth	533	668	716
4. General Public and Special Programs:			
a. National:			
(3) Treatment trials and therapy, information services	7,017	10,014	10,846
SUBTOTAL, National	7,017	10,014	10,846
b. Regional, state, and local	9	540	820
SUBTOTAL, Gen. Pub. and Spec. Prog	7,026	10,554	11,666

Category	FY 1989 Bud. Auth.	FY 1990 Appropriation	FY 1991 Estimate
5. Health-Care Workers and Providers:			
a. Education and training centers	999	1,249	1,342
b. Other types of training	1,110	1,164	1,264
SUBTOTAL, Health-Care Workers and Providers	2,109	2,413	2,606
SUBTOTAL, Information and education/preventive services	12,447	16,336	17,784
TOTAL, RISK ASSESSMENT AND PREVENTION	120,389	142,534	154,799
V. PHS-Wide Activities:			
C. Construction (PHS Facilities)	4,900	14,765	16,500
TOTAL	602,294	743,532	800,164

Acquired Immunodeficiency Syndrome

NIH continues to expand laboratory and clinical research to prevent and treat human immunodeficiency virus (HIV) infection. The President's FY 1991 Budget seeks a 7.6 percent increase for NIH's HIV efforts. Basic research in virology, molecular biology, and immunology has rapidly resulted in new information about the structure of the virus, its genetic variability, and the immune mechanisms triggered by infection. Clinical evaluations of vaccines, drugs, and therapies for HIV-related infections and cancers have resulted in new and better treatments. The following descriptions, organized by functional category, highlight a few scientific advances in the field of AIDS research.

I. Basic Science Research:

Biomedical Research:

The FY 1991 President's Budget provides $180,061,000 for Biomedical Research. Research in this area provides the basic framework for much of the research conducted in the other functional categories.

The expression of HIV in infected human cells is greatly increased through the action of two essential HIV regulatory proteins, tat and rev. Work has progressed in synthesizing large quantities of the tat and rev proteins to study the precise mechanisms of HIV gene regulation. In vitro systems are being developed to study the activation of regulatory genes by proteins such as tat and rev, to characterize the structure of the molecules involved, and to quickly and specifically detect their presence in human cells. In a related system, scientists have generated transgenic mice which express the tax protein, one of the regulatory proteins of HTLV-I and HTLV-II controlling viral replication. It has been determined that an oncogene is selectively activated in some tissues of these tax transgenic mice. This suggests that the oncogene and the protein may play a role in tumorigenesis in these animals. These results may shed light on the development of human malignancies associated with retroviral infection.

AIDS patients infected with HIV are also invariably infected with other agents such as oncogenic DNA viruses and other human retroviruses. Due to the long latency period of HIV, co-infections associated with AIDS may be responsible for the activation of the HIV provirus, immune activation and the progression of the disease. Also, it appears that a gene of CMV can activate the HIV-1 promoter leading to increased expression of HIV-1. This observation suggests an important co-factor role for CMV and other herpesviruses including human herpes virus 6. Studies to understand the role of these viruses in the activation of HIV expression and the progression to AIDS will continue in order to support the development of treatment modalities for patients infected with HIV.

The latency period between initial infection with HIV and the development of antibodies has recently been an area of active research. The polymerase chain reaction (PCR) technique will be used to detect HIV provirus in lymphocytes obtained serially from seroconverters in studies such as the Multicenter AIDS Cohort Study.

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Success in the basic biology area of AIDS research has been marked by two advances: (1) development of the first crystals of CD4, the protein recognized to serve as the receptor for the AIDS virus on host cells; and (2) progress on the expression and purification of the integration protein of HIV. The rapidly mutating HIV has also been found not to proofread its own RNA:DNA copying very well, making it difficult to study the virus' molecular biology and to design treatments. Current studies of how this enzyme makes errors may provide useful information for designing drugs and vaccines to treat or prevent the disease.

The viral etiology of AIDS-related malignancies is being actively investigated. The molecular interactions between viral and cellular genes involved in host cell growth regulation are being studied to elucidate the process in carcinogenesis.

Recent studies involving candidiasis, the most prevalent oral lesion in AIDS, indicate that the presence of this and other opportunistic infections is not due to unique or particularly virulent strains of microorganisms, but is the result of defective host mechanisms. The second most prevalent oral manifestation of HIV is "hairy leukoplakia," a whitish lesion occurring on the surface of the tongue that is believed to be caused by Epstein-Barr virus. This condition is considered predictive of frank AIDS.

An important issue to be resolved is the role of saliva and the oral cavity in the transmission of HIV. HIV can be recovered from the oral cavity and has been found in parotid saliva. However, the mouth and saliva do not appear to be routes of viral transmission and it has been demonstrated that submandibular gland secretions can inhibit the ability of HIV to infect lymphocytes.

Many basic research questions about HIV-related disease processes in the lung remain unanswered. Further research on lung complications associated with HIV infection will provide greater insight into the early disease processes and aid in the understanding of events that occur in the transition from healthy to diseased lungs in HIV infected individuals. A long-term multicenter prospective cohort study of the pulmonary complications of HIV infection has been jointly developed and initiated by NIAID and NHLBI.

Since the identification of HIV, the NIH has supported research to protect the safety of the Nation's blood supply. In addition, an understanding of the development of AIDS in hemophiliacs and other patients who acquire the virus through transfusion of blood and blood products has been sought. These efforts have contributed to the development of more sensitive tests and more effective screening procedures.

Other recent studies indicate that: (1) HIV-infected children sometimes suffer from gastrointestinal problems, such as chronic diarrhea, that may be caused directly by HIV; and (2) HIV virus can be transmitted in skin grafts used to cover wounds in severely burned patients. Investigators using the polymerase chain reaction technique have been able to detect HIV in skin biopsy tissue. This ability will make skin grafting a safer procedure.

In additional areas, a collaborative project is planned between NIAMS and the U.S. Army to examine: drug reactions; infectious complications; the effects of HIV infection on the normal bacterial population of the skin; and the extent to which the skin harbors potentially harmful organisms in various stages of HIV infection. In another related study the association of HIV infection and certain rheumatic and musculoskeletal diseases and manifestations will be examined.

The National Chimpanzee Breeding and Research (NCBR) Program was initiated in September 1986 to ensure the survival of the chimpanzee and its availability to researchers by creating colonies of chimpanzees. The chimpanzee is the only animal species in which HIV has been found to survive.

Neuroscience and Neuropsychiatric Research:

The FY 1991 President's Budget provides $21,669,000 for Neuroscience and Neuropsychiatric Research. Neurological symptoms are recognized in about half of the patients with AIDS, many of whom develop the devastating AIDS dementia complex. Post-mortem studies reveal that as many as 80 percent of AIDS victims may have neurological involvement.

The mechanism by which the human immunodeficiency virus (HIV) injures the nervous system is unknown. Previous work by intramural investigators has suggested that brain cells are killed indirectly by gp120, the external envelope protein of HIV. However, recent work confirms that in fact, gp120 does not act directly on brain cells, but rather, it interacts with the supporting cells of the nervous system which normally produce vital neurotrophic substances. Other studies suggest that further damage may occur either by direct viral infection of brain cells causing alterations in the metabolism of the affected elements, or indirectly through the toxic action of viral or cellular products.

HIV has been isolated from cerebrospinal fluid, brain tissue, spinal cord, and peripheral nerve. Further, HIV genetic material has been identified in nervous tissues by hybridization, electron microscopy, and other sophisticated laboratory techniques in patients with neurological manifestations of AIDS.

It has been generally accepted that a CD4 receptor must be present on a cell surface for the AIDS virus to attach to and penetrate the cell. Recent studies using cells derived from human fetal dorsal root ganglia and two different human brain tumors grown in tissue culture indicate that these cells can be infected even though they lack a CD4 receptor; further research will pursue this lead.

Another study on HIV infected individuals is investigating the concentration of quinolinic acid (QA), a metabolite of L-tryptophan, in the cerebrospinal fluid. The concentration of QA correlates with the severity of the AIDS dementia complex. Further studies on the role of QA in diagnosis and its action in the pathogenesis of AIDS dementia will be carried out.

Clinical and immunological studies of patients with HTLV-1 associated spastic paraparesis, polymyositis, and encephalomyeloneuropathy have drawn a

direct link between this virus and the progression of neurological disease. In addition, culture experiments appear to demonstrate a cooperative effect of HIV-1 and HTLV-1 coinfection in certain T-cells.

The relationship between HIV-1 and HTLV-1 infections will be studied both at the neurobiological and molecular levels. Experiments to test whether viral non-structural regulatory proteins which act together to enhance infection are significant factors in the pathogenesis of AIDS.

A longitudinal study in collaboration with the Bethesda Naval Hospital has been established to conduct tests on the clinical, immunological, virological, and neuropsychological status of AIDS in newly seroconverted patients.

Other new studies will focus on the potential therapeutic effects of an inactivated HIV-1 vaccine which lacks the viral envelope proteins; and the role of HTLV-1 in other neurologically related disorders, for example, multiple sclerosis.

Behavioral Research:

The FY 1991 President's Budget will provide $5,172,000 for Behavioral Research. A majority of the behavioral research activities involve studies to assess behaviors which may influence the transmission of HIV or the natural history of HIV related diseases.

Therapeutic Agents:

The FY 1991 President's Budget includes $326,388,000 for Therapeutic Agents. This represents approximately 41 percent of the FY 1991 request.

A comprehensive program for the discovery and development of drugs with anti-HIV activity has been developed. This program includes three basic components: 1) a high capacity drug screen to assess compounds for activity against the HIV virus; 2) a laboratory-based effort for developing novel approaches to drug treatment; and 3) a program for the preclinical and early clinical development of drugs with promising anti-HIV activity. This program provides a unique resource because of its comprehensive approach to AIDS drug development.

It has been responsible for discovering and developing many of the investigational drugs available for the treatment of AIDS. For example, azidothymidine (AZT), the only approved drug, and dideoxyinosine (ddI), recently granted Treatment IND status for use in AIDS patients were both developed in this program. Additionally, a number of promising new compounds under clinical development, including dideoxycytidine (ddC) and the fluorinated versions of ddI and ddC, are in different stages of study to determine their efficacy and safety.

It is projected that the Preclinical AIDS Drug Screen will identify up to 100 compounds with anti-HIV activity each year. Decisions to proceed with further preclinical and clinical development are made by NCI's Decision Network, a committee comprised of NCI and NIAID scientists and clinical investigators. In the past year, 16 compounds have been reviewed and approved

by the Decision Network for further preclinical drug development. One of the most exciting aspects of these compounds is that many of them have unique structures and probably inhibit HIV through different mechanisms. This is critically important because experience in other diseases tells us that AIDS may be more effectively treated by drug combinations which block different points in the virus' life-cycle.

Of particular interest, is the recent finding that a common anti-clotting drug, dipyramidole, widely used in the treatment of cardiovascular diseases, appears to significantly increase the ability of AZT to inhibit replication of the AIDS virus in in vitro experiments. In another project, investigations are underway into the collection and isolation of natural products with anti-HIV activity. This project has recently produced a new class of compounds with anti-HIV activity from cyanobacteria.

One of the most exciting new drugs to emerge from the Preclinical Drug Screen is dideoxyinosine (ddI). During the past year, a Phase I study of ddI revealed that this drug has low short term toxicity and, unlike AZT, it does not cause significant bone marrow toxicity. In another Phase I study, dideoxycytidine (ddC) was demonstrated to have a markedly different spectrum of toxicity from AZT. Dideoxycytidine causes comparatively little bone marrow suppression, but significant peripheral neuropathy. The study also indicated that ddC is well absorbed form the stomach and achieves good penetration into the central nervous system where HIV is often harbored.

Neurological complications strike about half of all AIDS patients, leaving many extremely disoriented for long periods of time. There is a special need for drugs that can assail HIV in the brain. Researchers are now evaluating three newly synthesized derivatives of ddC. Each ddC derivative is designed to cross the tightly woven network of protective capillaries which encases the central nervous system, called the blood-brain barrier.

A new recombinant protein has been produced that combines that portion of the CD4 molecule that attaches to the HIV virus with a powerful bacterial toxin, pseudomonas exotoxin (PE). This protein, termed CD4-PE, can attach to and kill HIV-infected cells in culture. Current studies are in progress to test the effect of the CD4-PE recombinant protein on different types of normal and HIV-infected cells.

Scientists are also studying the ability of the bone marrow stimulator granulocyte macrophage colony stimulating factor (GM-CSF) to offset the bone marrow toxicity of AZT. In the past year, 10 patients have been treated and preliminary results indicate that the combinations of AZT plus GM-CSF can be tolerated for more that 14 weeks and may be less toxic that AZT given alone.

The intramural AIDS program at NIH conducts early clinical testing on promising anti-HIV therapies in adults and children. Over the past year the intramural program has tested a number of new drugs including several biologic response modifiers (BRMs). These molecules include the lymphokines which are important in orchestrating the immune response.

Over the past few years, substantial progress has been made in the development of medications specifically directed toward the underlying retroviral infection. Several investigations have suggested that the

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administration of HIV hyper-immunoglobulin to individuals with AIDS may increase neutralizing antibody levels and prevent progression of disease. A new initiative will support research on the use of HIV immunoglobulin as treatment for HIV infection.

There has been significant emphasis placed on the testing of anti-HIV drugs in pediatric patients. This is a very high priority because the number of pediatric HIV infections are increasing rapidly due to the problem of drug use in women of child-bearing age. In the pediatric population, HIV causes a high incidence of brain dysfunction, including loss of normal brain development in very young children. A recent study in symptomatic HIV infected children examined the concentrations of AZT in the central nervous system. Dramatic improvements occurred in all 13 children who had significant brain dysfunction prior to treatment. This is the first demonstration that AZT is beneficial in children with symptomatic HIV infection.

In another pediatric study, ddC and ddI are being tested in children with symptomatic HIV infection. The children treated with ddC showed decreases in their viral p24 antigen levels and increases in the number of T4 lymphocytes. Three of the children who presented with brain dysfunction showed clinical improvement. Additionally, studies are being conducted looking at combination therapy, such as with ddC and AZT.

Research is ongoing to develop better treatments for HIV infected infants and children. Scientist have continued to investigate the role of intravenous immunoglobulin (IVIG) in preventing bacterial infection in HIV positive children.

To provide an optimal research and treatment assessment system, efforts are underway to unite NICHD pediatric AIDS clinical trials network with the pediatric AIDS network supported by the NIAID. The union of these two efforts will allow NICHD and NIAID to conduct clinical trials on anti-retroviral and other therapies in mothers, infants, and children throughout the U.S. Through this unified network, the vast majority of HIV-infected children and pregnant women will have access to clinical trials and to state-of-the-art research and care.

Efforts to enhance participation by the pediatric HIV infected population in clinical trials will be continued. The Community Program for Clinical Research on AIDS will expand its efforts to further increase minority participation in clinical trials.

Much of the treatment research supported by NIH is centered around a large network of multicenter clinical trials which evaluate potential AIDS therapies. These studies are assessing the safety and efficacy of new drugs and drug combinations in patients at various stages of HIV infection.

The National Cooperative Drug Discovery Group (NCDDG) investigators established a simple, rapid assay to screen a large number of synthetic compounds and natural products for their ability to inhibit HIV tat function. The group has examined approximately 7,000 compounds to date and has identified a lead compound with anti-tat activity.

Modeled after the highly successful NCDDG program, the National Cooperative Drug Discovery Group Program for the Treatment of Opportunistic Infections Associated with AIDS (NCDDG-OI) was launched in FY 1990 to support research on opportunistic infections.

A combination of two clinically available drugs, clindamycin and primaquine were identified by investigators as exhibiting excellent activity against Pneumocystis carinii both in vitro and in vivo. This combination is undergoing clinical evaluation. In another related study, based on the finding that P. carinii may be a fungus rather than a protozoan, contractors have developed a synthetic growth medium which will support the growth of P. carinii in the absence of other cells.

Future studies to investigate abnormalities of the lung in individuals with HIV infection will further evaluate the phenomenon of decreased lung glutathione levels. This research will evaluate aerosolized glutathione as a potential agent for augmenting pulmonary extracellular glutathione levels in HIV antibody-positive individuals. The current Phase II trial of aerosolized interferon, an agent which has a pivotal role in the regulation of immune processes, will continue.

Cytomegalovirus (CMV) retinitis is an opportunistic infection of the retina that occurs in more severely immunocompromised AIDS patients. Currently, the antiviral drug ganciclovir is the only drug licensed in the U.S. for the treatment of CMV retinitis. However, ganciclovir is most effective at dosages that frequently produce bone marrow suppression as does AZT. Consequently, the two drugs cannot be used concurrently. Foscarnet, an investigational drug for CMV retinitis, has shown activity against HIV as well as herpes viruses, such as CMV. The major objectives of the clinical trial are to compare the relative safety and efficacy of foscarnet with that of ganciclovir for treating CMV retinitis, and to evaluate the relative effectiveness of foscarnet and ganciclovir therapy on patient survival.

The testing of drugs as potential treatments for HIV infection and its sequelae is a key imperative of HIV research. Scientists through the AIDS Clinical Trial Group (ACTG) have reported significant advances in the treatment of HIV infection. Protocol 019 furnished the first evidence that zidovudine (AZT) can delay disease program in HIV-infected asymptomatic people with T cell counts of less than 500. Another advance in AIDS treatment research this year emanated from protocol 016, which showed that participants with early AIDS Related Complex (ARC) progressed to advanced ARC or AIDS significantly more slowly while on AZT than placebo.

NIAID will sponsor a consensus conference to assure optimal technology transfer from protocols 016 and 019. The conference will establish recommendations for the use of zidovudine therapy in routine medical practice for patients with early HIV infection.

The general clinical research centers (GCRCs) are a major network supporting a wide array of AIDS-related clinical studies. The GCRCs undergird many of the studies conducted by the AIDS Clinical Trial Units, the Multicenter AIDS Cohort study, and the National Cooperative Drug Discovery Program for the treatment of AIDS. One of the GCRCs housed a study in which investigators attempted to define opportunistic infections that are most

prevalent and linked with the highest mortality rate in an urban pediatric population. As in the adult population, Pneumocystis carinii pneumonia (PCP) was the most frequently reported opportunistic organism with a high mortality rate linked to both clinical presentation with acute respiratory failure and co-infection with CMV.

Because many of the AIDS projects require highly purified HIV proteins, a central facility has been established during the past year to produce such proteins in sufficient purity and quantity for structural, physio-chemical, and pharmacological studies. The laboratory is now being constructed on the NIH Campus in Bethesda, MD, in the new Building 6B and will be ready for occupancy in February 1990.

The NCI supercomputer continues to play an important role in the study of the HIV virus. Last year special software programs were developed enabling scientists to predict the structure of the HIV genome and to look for correlations between certain structural features and their possible functional correlates.

The Intramural AIDS Targeted Antiviral Program has given us a number of major new findings over the past year. The complete three-dimensional structure of interlukin-8 in solution was determined by nuclear magnetic resonance. This is a key protein in the response of the immune system to HIV infection. Also noteworthy, the discovery that a commonly used drug, dipyridamole, increases the antiviral effect of AZT while reducing its toxicity. A clinical trial using this combination therapy is being planned.

Vaccines:

The FY 1991 President's Budget provides $86,130,000 for vaccine development and related expenditures. The support of research aimed at expediting the development and testing of AIDS vaccines is a high priority. Basic research studies are expanding knowledge of the mechanisms of immunity to HIV as well as information on the most promising candidate vaccines. For AIDS vaccines, development of adjuvant technology has also become an important focus in efforts to potentiate immune responses to candidate vaccines.

A recent discovery has been the identification of the first antigenic site of HIV recognized by cytotoxic or killer T cells. This cytotoxic T cell peptide and three HIV-derived peptides recognized by T helper cells have been tested in humans and found to be capable of eliciting an immune response in normal individuals subsequently immunized with a recombinant HIV protein. Asymptomatic HIV-infected individuals also developed an immune response from these peptides.

Perhaps the most dramatic advance in AIDS vaccine development thus far is the recent evidence from several animal studies that experimental lentiviral vaccines, using novel adjuvants, can protect against the establishment of infection and AIDS-like disease. These studies demonstrate the scientific feasibility of AIDS vaccine development.

The NIAID Vaccine Evaluation Units, a network of six contractors serving as a national resource for the evaluation of vaccines, are presently conducting Phase I testing of two experimental AIDS vaccines. A major hurdle

in vaccine development is the genetic variability of HIV. The NIAID has expanded the efforts of the HIV genetic sequence database to clone and sequence strains of HIV from different geographical locales and from different time points in infected individuals in order to obtain a better understanding of the magnitude of genetic variation and its impact on vaccine development.

The vaccine effort will be enhanced by beginning the process of developing the capacity to undertake Phase III efficacy trials of AIDS vaccines. Increased support of basic research particularly in immunological areas of T-lymphocyte activation and novel vector construction to provide reagents and research resources to test experimental AIDS vaccines in appropriate animal models will be supported.

The Primate Research Centers are continuing their activities in AIDS research. Recently, investigators at the Delta Regional Primate Research Center found that immunization with a killed whole SIV vaccine prevented infection and disease in 8 of 9 rhesus monkeys experimentally exposed to SIV.

Research Enhancement:

The FY 1991 President's Budget provides $9,445,000 for Research Enhancement which includes training and extramural construction.

The large increases in the NIH-supported AIDS research programs have created needs for additional research space; upgraded clinical, laboratory, and animal facilities; and related equipment necessary for the safe and efficient conduct of AIDS research. In order to meet these needs, the Congress provided $23,935,000 in FY 1988 and $4,940,000 in FY 1989 for a new program--the Research Facilities Improvement (RFI) Program. These funds supported some 50 projects to provide for repair, renovation, modernization, and expansion of existing facilities that are being used for the conduct of AIDS or AIDS-related research, and for the purchase of associated equipment.

In FY 1991 the NIH will continue its efforts in the AIDS Research Loan Repayment Program. This program will enhance the recruitment and retention of NIH scientist conducting AIDS research. Notice of this program was published in the Federal Register on November 8, 1989.

II. Risk Assessment and Prevention:

The FY 1991 President's Budget provides $154,799,000 for Risk Assessment and Prevention.

Preliminary analyses indicate that HIV-infected women transmit the virus to approximately 30 to 40 percent of their offspring, with premature babies appearing to be at three-fold higher risk than full-term babies. Remarkably, it has been shown that mothers who did not transmit HIV to full-term babies had very low or absent levels of antibody reactive to gp120, the HIV envelope glycoprotein. Further laboratory characterization of this observation is in progress.

In a collaborative study between NCI and NICHD, 250 pregnant women have been enrolled and approximately 40 percent are HIV-infected. HIV-infected

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women with advanced immunodeficiency have developed Pneumocystis carinii pneumonia and other opportunistic infections at a high rate, but there have been no marked increases in adverse pregnancy outcomes.

Spouses and long-term heterosexual partners of patients in various clinical stages of HIV infection are being followed in order to obtain a better understanding of risk factors for acquiring HIV and of disease progression. Among the spouses/partners enrolled, there was no difference between men and women in the seroprevalence of antibodies to HIV. Presence of HIV antibody in a spouse correlates directly with: the severity of HIV disease in the index case, the presence of p24 antigen in the index case, a low T4 cell count in asymptomatic index cases, presence of genital herpes or gonorrhea in the spouse, and the lack of condom use in the preceding year. The length or frequency of sexual contact and the types of sexual activity did not correlate with the presence of antibody to HIV in a spouse.

The Contraceptive Evaluation Program designed a mathematical model to determine the amount of protection condoms provide against HIV. The model demonstrates that for those at low risk of HIV infection, including the general non-IV drug-using heterosexual population of the U.S., the number of HIV infections prevented by the proper use of condoms will be greater than can be attributed to their failure.

A laboratory study was completed recently to evaluate the suitability of using condoms, and condoms plus spermicides, to prevent the transmission of HIV. The results of the in vitro condom testing program demonstrated that the current supply of condoms on the American market are of high quality and should provide a substantial degree of protection from HIV and other sexually transmitted diseases that are cofactors for HIV transmission. In another study, researchers found that teenagers who say they are able to talk with partners about condom use are more likely to actually report having used a condom at last intercourse.

Several large, multicenter epidemiologic research projects are underway. These studies are revealing the information on HIV transmission and course of the disease in various populations.

Epidemiologic studies show that over 43 percent of AIDS cases in the U.S. occur in non-whites. Infected women are disproportionately of minority background, and their prevention and treatment needs deserve special consideration. An estimated 90 percent of funds for the Women and Infants Transmission Study and 93 percent of funds for the Heterosexual HIV Transmission Study are devoted to populations underrepresented in clinical trials. The Multicenter AIDS Cohort Study (MACS) has specifically developed protocols to increase non-white participation in its longitudinal studies.

In a NCI study, in collaboration with the National Institute on Drug Abuse, 1,766 parenteral drug users were recruited from treatment programs from across the U.S. and evaluated for prevalence of HIV and/or HTLV-I/II. Twenty-one percent had HIV antibodies, with higher rates among blacks and hispanics than whites. HTLV prevalence increased with older age in all racial groups but was similar in males and females.

Studies of HIV infection in people over 60 years of age will continue with special emphasis on the changes seen in certain T cell subsets in the peripheral circulation. .In this age group there is a remarkable complete absence of a subset of toxic T lymphocytes not seen in younger patients. These cells play an important role in the defense against HIV and in the elimination of HIV infected tissue.

The "AIDS deficit" was first observed in mid-1987 when less than the expected total number of cases were reported. This was initially seen in several high risk groups, and the deficits are greatest in groups expected to have the best access to medical care. For example, white homosexual and bisexual men had a deficit of 25 percent in the last half of 1988, compared to 14 percent for blacks. Deficits have been seen among homosexual and bisexual men, homosexual intravenous drug users, hemophiliacs and transfusion recipients. The deficits increased over time from mid 1987 through the end of 1988, as one would expect as increasing numbers of patients began treatment.

An international registry of AIDS patients has been established for persons with documented dates of HIV seroconversion in order to evaluate co-factors and trends in AIDS risk. Within risk groups, time-to-AIDS was the same in all geographic areas and among early, i.e., pre-1985, and later seroconverters. Children with hemophilia progressed to AIDS more quickly than did adults, and homosexual men progressed to AIDS more quickly than did adult hemophiliacs because of an excess of Kaposi's sarcoma in the former group.

Several studies have assessed the safety of the blood supply by determining the frequency with which HIV-1 infection is transmitted by transfusion of seronegative blood. Results indicate that the risk of HTLV-I seroconversion after receiving blood that was negative for HIV-1 antibody was nearly tenfold greater than the risk of HIV-1 infection, 0.024 percent versus 0.003 percent per unit. This study indicates the desirability of screening for HTLV-I.

Research results are of little value if they are not easily accessible to scientists and clinicians, therefore the National Library of Medicine has laid the foundation for a data bank that will contain information on the results of research with respect to AIDS conducted in the U.S. and abroad. This comprehensive AIDS information service, will provide scientists, physicians, and other health professional faster access to more information on AIDS research, diagnosis, treatment, control, and prevention activities.

The Office of AIDS Research will initiate a series of AIDS technology transfer meetings to enhance the sharing of information on safety, AIDS technology, and AIDS related research at regional meeting throughout the U.S.

The NIH is also in the midst of designing a centralized AIDS Research Information System (ARIS) to track and categorize the funding for AIDS research.

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V. PHS Wide Activities:

Construction (PHS) Facilities:

The FY 1991 President's Budget includes $16,500,000 for the renovation, modernization, and expansion of existing facilities and the design and construction of new facilities related to AIDS research activities.

Projects that are currently being designed or constructed include an addition to the Clinical Center, renovating the Twinbrook II Building to house key components of the NIAID AIDS research program, and a new building for NCI at the Frederick Cancer Research Facility.

Planned projects include a retrovirus laboratory, a primate facility, an expanded medical intensive care unit in the Clinical Center to accommodate AIDS patients, and various renovations to existing AIDS laboratories.

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